UiT The Arctic University of Norway

Faculty of Health Science
Department of Pharmacy

Optimising drug therapy in older patients

Exploring different approaches across the patient pathway

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A dissertation for the degree of Philosophiae Doctor July 2022

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Be selective in your battles, sometimes peace is better than being right[1].

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«Alt håp var ikke ute. Han begynte å hente krefter fra et sted inne i seg selv.»[2]

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[1] Chief John Shenandoah c. 1706 - March 11, 1816 "Pine Tree Chief" of the ONEIDA.
[2] Olaf Havnes, Ørnens sønn (1996)

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Not having heard something is not as good as having heard it; having heard it is not as good as having seen it; having seen it is not as good as knowing it; knowing it is not as good as putting it into practice[3]

[3] From *Xunzi,* Xun Kuang's *Ruxiao* ("The Teachings of the Ru")

Abbreviations

AC: Anticholinergic

ATC: Anatomical Therapeutic Classification

CI: Confidence Interval

DAG: Directed Acyclic Graph

DDD: Defined Daily Doses

DRP: Drug-Related Problem

GP: General Practitioner

HR: Hazard Ratio

IMM: Integrated Medicines Management

IRR: Incidence Rate Ratio

LOS: Length Of Stay

NorPD: Norwegian Prescription Database

NPPC: Norwegian Pharmaceutical Product Compendium

NPR: Norwegian Patient Registry

OR: Odds Ratio

PDI: Post-discharge Institutionalisation

RCT: Randomised Controlled Trial

SD: Standard Deviation

SED: Sedative

WHO: World Health Organization

WOMBAT: Work Observation Method By Activity Timing

List of papers

N	Paper	Status
I	Is anticholinergic and sedative drug burden associated with post-discharge institutionalization in community-dwelling patients acutely admitted to hospital? A Norwegian registry-based study	Submitted June 29th, 2022, Pharmacoepidemiology & Drug Safety, currently under review.
II	Interdisciplinary collaboration across secondary and primary care to improve medication safety in the older (IMMENSE study): study protocol for a randomised controlled trial	Accepted December 17th, 2017 Published: BMJ Open January 23rd, 2018
III	Intervention fidelity and process outcomes of a pharmacist-led interdisciplinary intervention to improve medication safety in older hospitalized patients	Accepted November 23rd, 2021 Published: J Clin Pharm Ther. Dec 21st 2021
IV	Time distribution for pharmacists conducting a randomized controlled trial– an observational time and motion study	Accepted April 15th, 2021 Published: PLoS One, April 30th, 2021.

Abstract

Background - Drug therapy contributes to healthy ageing but has a key duality: It prolongs and can improve quality of life, but drugs can also cause serious harm. Harm from drugs include falls, cognitive decline, lowered quality of life, hospitalisation, and death. Older patients are especially at risk for harm from drug therapy, therefore optimising drug therapy is imperative for this group.

Aim - To generate new knowledge of drug therapy optimisation for older patients by exploring the impact of drug burden and investigating different approaches to optimise drug therapy across the patient pathway.

Methods - This thesis used data from The Norwegian patient registry, The Norwegian Prescription Database and data collected in a randomised controlled trial (RCT). Observational data of the delivery of the RCT-intervention was included. In Paper I the association between anticholinergic (AC) and sedative (SED) drug burden and post-discharge institutionalisation (PDI) was assessed using multiple regression. Paper II described an RCT investigating the effect of an in-hospital pharmacist intervention. Paper III presented the fidelity and process outcomes of the intervention (Paper II). In Paper IV, an observational tool was developed and time distribution for the pharmacists running the RCT examined.

Results - Number of drugs used before hospitalisation was mean 7.11 (SD 4.09) and at hospitalisation median 6.0 (range 4-9). Prevalence of AC/SED drugs was 45.5%. All measures of AC/SED drug burden was significantly associated with PDI. The number of AC drugs were most sensitive (OR 1.13, per AC drug), and the DBI most challenging to apply. The clinical pharmacist contributed to identify and solve discrepancies for 72% of the patients (median 1) and DRPs for 94.6% of the patients (median 4), and the acceptance rate was 67%. Intervention fidelity at admission was 100%, and 57% overall. The pharmacists advanced communication of drug therapy across the patient pathway. About 41% of pharmacist time was spent on administrative RCT-tasks and the estimated intervention time was >3.5 hours/patient.

Conclusions - The drug burden is high in older patients acutely admitted to hospital in Norway and assessing AC/SED drug use can potentially reduce the risk of PDI. The in-hospital pharmacist intervention contributed to drug therapy optimisation and facilitated communication across the patient pathway. These measures can contribute to optimisation of drug therapy but are time consuming and costly. It is essential to establish models for drug therapy optimisation across the patient pathway, with emphasis on primary care.

1 Introduction

There is an expected increase in old people worldwide. From 2015 to 2050, the number of people >60 is predicted to increase by more than 50%. This rise implies that by 2050, a third of the European population is 60+ years (1). To address challenges arising from the worldwide rise in life expectancy and increase in older people, the World Health Organisation (WHO) has published a global strategy and action plan on ageing and health (1, 2). WHO defines healthy ageing as 'the process of developing and maintaining the functional ability that enables well-being in older age'(3). A pivotal component in ageing and health is drug therapy (4).

Drug therapy displays a key duality. On one hand, drug therapy prolongs life span and reduces mortality, it relieves symptoms and increases the quality of life (5). On the other hand, drug therapy is a burden and can cause serious harm (6). Older people are particularly vulnerable to and frequently experience harmful effects of drug therapy. These multifaceted challenges may be caused by multimorbidity, polypharmacy and unpredictable, age-related changes (4). In addition, transitions across health care levels for older people can affect the outcome of drug therapy (7). In sum, these challenges with drug therapy increase societal costs and health care utilisation.

To enable healthy ageing, optimising drug therapy may have an influence. Drug therapy optimisation must be studied in the context of national health care systems. In Norway, a 'National action plan for patient safety and quality improvement' addresses the need for emphasis on improving the quality of drug therapy and patient safety (8). By 2016 no studies investigating the effects of drug burden on health care utilisation nor on integrated pharmacist interventions to optimise drug therapy for older hospitalised patients, in Norway, had been published.

Therefore, this thesis addresses drug therapy optimisation for older patients in Norwegian health care. It focuses on measures to improve the quality of drug therapy and how pharmacists can facilitate more efficient treatment and improve health outcomes for older patients.

1.1 Older patients

Older patients (9) are characterized by heterogeneity in function, morbidity, and the presence of signs of ageing (10, 11). The progression of ageing and what organs are affected first is individual (10), impacted by genetics, environmental factors, and behaviour (11). Older patients are particularly vulnerable to drug therapy because of age-related pharmacokinetic and pharmacodynamic changes. These changes alter drug utilization processes such as absorption, distribution, metabolism, and elimination (4, 12). Finding markers to identify biological age, has proven difficult (13).

Ageing affects an individual's intrinsic capacity, "the mental, and physical capacities that a person can draw on". Intrinsic capacity involves areas such as mobility, hearing, vision, and cognitive capacity. Low intrinsic capacity can increase susceptibility to disease (14), while intrinsic capacity, biological age, and morbidity, together with environmental factors affect an individual's functional ability (14), i.e., to what extent an individual can "be and do what they value". To "develop and maintain functional ability" is a cornerstone of WHO's initiative of healthy ageing. Healthy ageing emphasises person-centred integrated care where one sector is health care (15).

1.2 Health care and health care delivery

Health care, 'services provided by a country or an organization that involve caring for people's health and treating people who are ill' (16), is provided on different levels. Primary care is the person-focused health care provided by clinicians over time, outside hospitals, and include elderly care such as institutions (i.e., rehabilitation and nursing homes), general practitioner (GP) and home care. It is a low threshold contact which can be an entry point to more specialized and complex care levels, i.e., hospitals (17). Patients usually get access to hospital services through referrals from their primary care physician or emergency clinics. Hospitals provide in- and outpatient care. Inpatient care implies admission to the hospital for overnight stays and close monitoring by health care personnel. Differences in guidelines, structure, and financing result in disparities in available health care across borders (18). In Scandinavian countries, the publicly funded health care system is decentralized and differentiated (19-21) following a principle of delivering care at the lowest, most effective level (21). Responsibilities for the patients tend to be divided, with several parties involved (19, 20).

In Norway, there is a principle of equal access to health care (20) and patients have a statutory right to necessary health care (22). Primary care is a municipal responsibility, while the specialised hospital sector is a governmental responsibility (20). The public hospitals are organised in hospital trusts, each owned by one of four regional health authorities (21).

Norway has 18 central health registries to measure the quality of health care delivery for the population (21). The Norwegian Patient Registry (NPR) holds identifiable data and comprises information on all in and outpatient hospital stays in Norway (23). The Norwegian prescription database (NorPD) on the other hand, contains anonymized data about prescription drugs dispensed from Norwegian pharmacies (24). It is a national aim to increase the availability of data to encourage more efficient utilisation of data, also for research (25).

1.3 Health care utilization and the patient pathway

A patient pathway describes the patients' path within healthcare and consist of any steps a patient can experience when managing disease. Steps can comprise several settings, transitions between care levels, within care levels and can be carried out by different health care providers, delivering various services (21). Old patients' patient pathway is affected by the structure of the healthcare system, for example, the Scandinavian model has patients frequently transitioning within and between care levels (19, 20). The patient pathway studied in this thesis concerns hospitalisation and consist of the following steps: i) time preceding hospitalisation in primary care (**pre-admission**), ii) **admission** to hospital care, iii) **hospital stay,** iv) **discharge** and v) primary care **post-discharge,** including post-discharge institutionalisation (PDI). Steps ii and iv are transitions between care levels. See Figure 1.1.

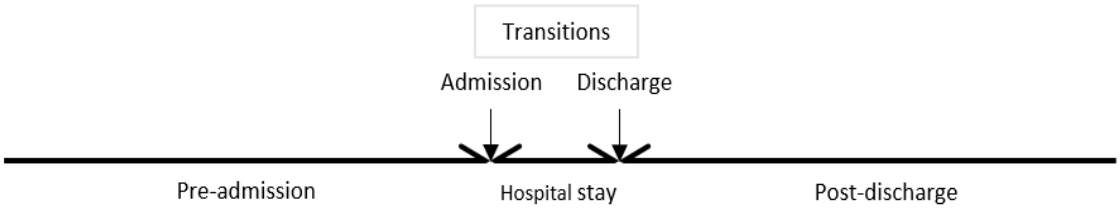


Figure1.1. An overview of the patient pathway in connection with hospitalisation, including transitions. **Pre-admission:** the time before hospital admission, here: primary care, **admission**: the transfer from primary care to hospital, **hospital stay** patient admitted to hospital, **discharge:** the transfer from hospital to primary care, **post-discharge:** primary care: home-dwelling or post-discharge institutionalisation.

High age is associated with high health care costs (26). In Norway, four out of ten hospital bed-days in 2020 were occupied by patients >70 years, increasing to almost six of ten if the

age span includes 60–70 year-olds (27). When discharged from the hospital, readmissions and PDI are common outcomes (28, 29). 'Ageing in place' is considered beneficial for the patients (30), and older patients prefer to age at home (31). Identification of patients at higher risk for PDI could delay institutionalisation or improve the transition (32). A first step would be to assess potential associations between exposures known to affect older patients negatively and adverse outcomes.

Institutionalisation, either independently or following hospitalisation, is strongly affected by prior hospital and nursing home use (33), age, and factors following cognitive and/or functional decline such as dementia, falls and functional dependency (34, 35). Readmissions to hospital are affected by frailty and limited activities of daily living (36). Drug therapy is rarely included as an explanatory variable when predictors for hospitalisation, readmissions to hospital and institutionalization are investigated. Luppa et al. identified drug therapy as an explanatory factor in four of 36 studies aiming to find predictors for institutionalisation (34). Harrison et al. found that two of 23 studies aiming to predict discharge to institutional care included drug therapy (29). Wallace et al. reviewed models to predict risk for hospitalisation and identified drug therapy as a factor in six of 27 models (37). When included, drug therapy is often included as the number of drugs (29, 34, 37). Omitting drug therapy as an explanatory factor might lead to conclusions based on the wrong terms since most older patients use drugs. In addition, drug therapy is an alterable factor, in contrast to e.g., chronic conditions. A differentiated approach to drug therapy might be in order, for example focusing on drug classes or properties known to be of higher risk for older patients.

1.4 Drug therapy in older patients

1.4.1 Prevalence and polypharmacy

Drug therapy is an indispensable part of health care, providing potential for treatment and/or prevention of diseases. Prevalence of disease increase with age, and chronic drug use is common in older patients (38). Among older patients in the USA, eight of ten have been found to use at least one prescription drug (39), while nine of ten Norwegian 65-year-olds used at least one (40). The use of multiple drugs, polypharmacy (41), is frequently seen in older patients (38, 39). Polypharmacy is commonly defined as five or more medications in use, but definitions range from ≥2-11 (41), which will affect the prevalence. For example, Young et al. found that 65% of older patients had polypharmacy, including what they defined as "minor polypharmacy" (2-3 drugs in use), while 49% used ≥ 4 drugs (38). Another study

found that 29% of older patients used >5 drugs (42), this increased significantly to over 35% over the next five years (39). Older patients admitted to hospital have been found to use between 6-9 drugs on average (43, 44).

1.4.2 Drug burden

Drug burden includes many dimensions (45, 46). Patient-reported drug burden includes management and social issues as well as health care system factors making living with drug therapy challenging. The burden is exacerbated by complexity of drug therapy regimens, unsuitable medications and barriers experienced in connection with health care services, such as waiting time, and missing, or contradictory, information regarding drug therapy (45). These factors affect the patient's views of and behaviour concerning drug therapy. For example, negative experiences can generate negative feelings about drug therapy, decreasing the likelihood of following a treatment plan (45, 46). Drug-related adverse events are described as the most challenging to experience. In addition, patients often handle a snowballing increase in drug burden (45). In this thesis, drug burden includes the number and characteristics of drug therapy in use and drug-related problems.

1.4.3 Anticholinergic and sedative drugs

Certain classes of drugs cause problems for older patients (47). Drugs with anticholinergic (AC) (48) and sedative properties (SED) (49) are among these. AC drugs inhibit the effect of acetylcholine, a major transmitter of nerve impulses in the central and peripheral nervous system, imperative for memory and cognition (50). AC drugs can cause side effects from several physiological systems, centrally and periferally (51), and include fall tendencies, cognitive dysfunction/delirium, incontinence/retention and dry mouth (48). SED drug therapy can cause side effects such as falls and cognitive decline (47, 52). The physiological mechanisms of cholinergic transmission and sedation an be altered in older patients, making them particularly at risk for AC/SED-related side effects. For example, AC side effects have been found seven times higher in older patients, compared to younger (48).

Nevertheless, AC and SED drugs are commonly used by older patients (53, 54). Factors associated with high prevalence of sedatives are female gender, high age, depression, loneliness and poor education (53, 55), and hospitalisation potentially increases exposure to these drugs (56). Older patients living in a nursing home are more frequently prescribed drugs affecting the nervous system, when compared to home-dwelling older patients (57). A high load of AC drugs is associated with an increased risk of adverse outcomes in older patients

(48), while sedative drug therapy is associated with an increased risk of fractures and cognitive decline (52, 58).

1.5 Drug-related problems

A drug-related problem (DRP) is defined as 'an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes' (59). DRPs can comprise adverse drug events, 'adverse outcomes that occur while the patient is taking the medicine' where causality is not necessarily involved, and/or adverse drug reactions which are "unintended responses, with normal doses' (60, 61). DRPs can emerge from over-, under- and mis-prescribing (59, 62).

Prescribing cascades (63-65) are a component of drug-related problems:. A cascade occurs when side effects from drug therapy are understood as new medical conditions, causing initiation of new drug therapy, potentially causing new side effects (63, 64). There are several cascades identified (64, 65). A clinical example is presented in Figure 1.2.

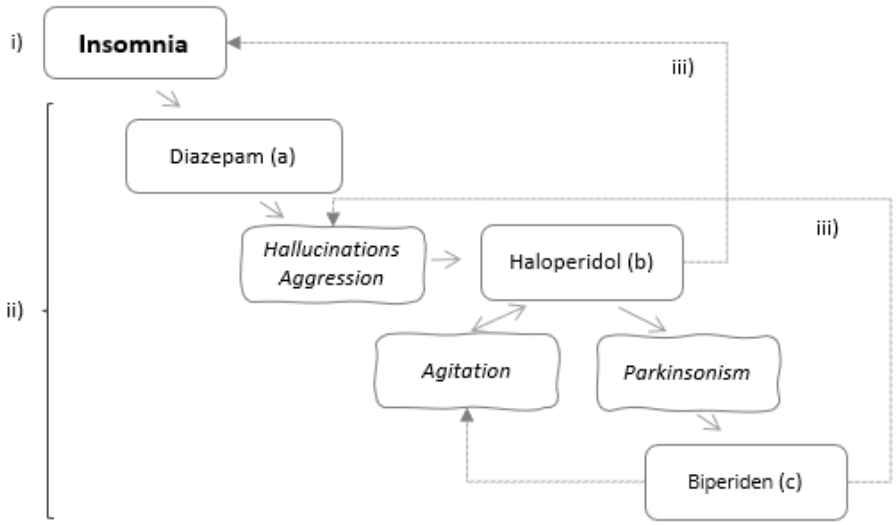


Figure 1.2. A prescribing cascade, initiated by treatment of insomnia: **a)** A benzodiazepine. Potential side effects: paradoxical reactions such as *hallucinations, and aggression*. **b)** An antipsychotic drug. Common side effects: *parkinsonism, agitation, insomnia, psychosis.* **c)** An anti-Parkinson drug. Potential side effects are *agitation, hallucinations, insomnia* (66). (Figure inspired by Alagiakrishnan, et al. (12)).

For a patient with an insomnia diagnosis (i), a prescribing cascade (ii) is initiated by the prescribing of long-acting benzodiazepines (a) with side effects (hallucinations, aggression) causing new prescribing of drugs (b,c), which, in turn, result in new side effects (agitation, parkinsonism), treated with anti-Parkinson drug therapy. In addition, the new drugs

potentially add to problems manifested upstream in the cascade (iii), although this is not a requirement of a cascade, it illustrates the complex nature of prescribing cascades. Identifying the drug initiating the cascade is essential.

Patient adherence is considered imperative to reach desired outcomes from drug therapy (67). Adherence is defined as "the extent to which a person's behaviour corresponds with agreed recommendations from a health care provider" (68), and non-adherence to therapy is a drug-related problem.Patient factors associated with lower adherence in old age are knowledge level, not experiencing symptoms of disease and concerns about or a desire to avoid side effects (69). Drug therapy factors associated with lowered adherence include the complexity of, and changes in the drug therapy regimen (69). Recent hospitalisation and the presence of multiple prescribers are also among factors affecting adherence negatively (70).

1.6 Prevalence and impact of drug-related problems

DRPs are frequently seen in older patients (71, 72). For older patients in ambulatory care, the median prevalence of adverse drug events has been found to be 18% (73). A Norwegian study found that 18.4% of patients above age 70 were prescribed at least one potentially harmful drug by their GP (74). For Norwegian patients receiving home care or living in nursing homes, these numbers were 25% and 31% respectively (75). In Norwegian nursing homes, three of four residents had drug-related problems considered clinically relevant (76).

The majority of hospitalised patients have one or more DRPs (77), and the average number of found DRPs range between 2-6.5 (43, 44, 78). DRPs give an increased risk of morbidity and hospitalisation (77, 79). Adverse drug reactions cause around 10% of hospital admittances (80, 81), while reports identify that 30 % of hospital admittances in older patients may be related to adverse drug events (82, 83). Non-adherence to in-hospital changes can increase the short-term risk of adverse events post-hospitalisation (84).

Many drug-related problems in older patients admitted to hospital are preventable (82, 85). Interventions aiming to reduce DRPs may have an impact on their prevalence and consequently lower adverse outcomes for this population.

1.7 Optimising drug therapy for older patients

Optimisation of drug therapy for older patients implies addressing a complete and complex picture of drug therapy (86). However, for this thesis, a narrower understanding is applied. Drug therapy optimisation is limited to individual drug therapy, comprising the elements of i)

quality of treatment, including identification of drug burden, DRPs and determination of optimal drug therapy and ii) implementation aspects, concerning factors affecting the drug therapy consequently used by the patient.

Quality improvement of drug therapy relies on an evaluation of the patients' clinical status, combined with pharmacological properties and principles for use. The individual patient's clinical and functional status should guide the choice of drug(s), dose, dosage frequency and form (87). Further, considering the patient's circumstances, function, and preferences is important to identify the patient's experience of quality and drug burden. The complexity and heterogeneity among older patients make this process challenging (88).

When optimising drug therapy, factors affecting implementation of drug therapy in use are imperative to consider. Knowledge lost in transitions between care levels results in insufficient information following the patient both to and from secondary care, leading to DRPs (89). Older patients and their caregivers weigh collaboration between settings as imperative for drug safety (90). Implementation of quality drug therapy is imperative to reach desired outcomes.

1.8 Drug therapy optimisation across the patient pathway

Factors involved in drug therapy optimisation change over time, thus optimisation should be an ongoing process (91). There are opportunities for interventions to address quality improvement and implementation aspects across all steps in the patient pathway (for patient pathway, see Figure 1.1). However, there is no consensus on when or where in the patient pathway interventions targeting drug therapy optimisation are most efficient. Traditionally physicians have been responsible for the prescribing and the assessment and evaluation of effects of patients' drug therapy. However, including pharmacists in interdisciplinary teams in hospital was suggested as beneficial to increase optimisation of drug therapy for older patients in the USA early in the 1960ies (92, 93). Since the start of 2000s, pharmacist have been introduced to different clinical settings across the patient pathway in Norway for drug therapy improvement (94).

Pharmacist interventions in Norwegian settings have shown potential in nursing homes (95), at admission to hospital (96), and in hospital (97, 98), with benefits continuing post-discharge (98). A thorough pharmacists' patient interview approach has been described to "fill a gap", making sure that significant drug-related problems are dealt with in-hospital (97). Several of

these studies describe pharmacist contributions into multi- or interdisciplinary collaboration in the setting investigated (95, 97, 98). Interdisciplinary collaboration can provide a potential for synergy between professions, potentially enhancing the optimisation process (99).

At the same time, there is a call for predictive tools to identify patients at high-risk for drug-related adverse outcomes (100). Screening is to "detect something prognostic (for example a risk factor), followed by an intervention, which in turn improves the outcome, such as quality of life or fewer complications" (101). Screening can aim at patient characteristics, such as frailty and comorbidities, or patients drug use, for example polypharmacy, or use of high-risk drugs. However, predictive value rely both on the presence of associations for a defined outcome, and interventions suited for the purpose. For older patients screening for a set of factors, i.e. as an index, has been found to work better than single variables (102). Still, developed screening tools to predict adverse outcomes in older patients are not satisfactory sufficient (103). Finding drug therapy indicators as tools to identify patients with increasing risk for undesired outcomes could contribute to the improvement of care (104).

1.9 Approaches to optimise drug therapy

1.9.1 Clinical guidelines

Available knowledge from research and practice is often specified in clinical guidelines as 'identified best practice' (105). However, despite drug users often being multimorbid and old, treatment guidelines have commonly been based on drug trials of single diseases, rarely including old individuals (106, 107). The treatment guidelines are commonly single disease based and the applicability to comorbid patients are questionable (108).

In Norway, the Norwegian Directorate of health is the executive function for the Ministry of Health and Care services. One responsibility is to gather knowledge, standardise information and give national advice (109). Currently, there are 74 national guidelines from the Norwegian Directorate of health, mostly single disease guidelines. No clinical guidelines target older patients as a group. National recommendations, on the other hand, has recommendations concerning physical activity and psychiatric disorders, for older people. Nevertheless, most of the disease specific guidelines also apply to older patients, such as dementia, cancer and stroke guidelines (110).

Following guidelines can pose a challenge, especially for older multimorbid patients. Boyd et al., demonstrated that for older multimorbid patients, following guidelines can cause excessive drug use (111), and there is potential for high-risk interaction between drugs in multimorbid patients following recommendations in guidelines (112, 113). This compromises the drug safety for the older patients.

1.9.2 Tools to identify inappropriate prescribing

To help clinicians optimise drug therapy among older patients, several clinical tools have been developed. Implicit lists, such as the Medication Appropriateness Index (MAI) (114), are based on clinicians' judgement, thus not standardised (115). In contrast, the explicit lists, are criterion based, standardised lists, facilitating the recognition of potentially inappropriate prescribing, or medication omissions (115). Listed criteria are usually consensus or expert based (115) since evidence for drug therapy for geriatric/old patients often is absent (106, 107). A 2018 review (116) identified 26 criterion based lists e.g., START/STOPP (117), BEERS (118) and EU(7)-PIM (119). The latter being a European initiative, to enable comparison between countries as well as being a prescribing guide. Furthermore, the NORGEP (120) and NORGEP-NH (121) for use in general practice and nursing homes respectively are criterion-based lists developed in Norway. In addition, there are tools that address specific drug categories considered potentially inappropriate for older patients, such as the Drug Burden Index (DBI) (122, 123).

1.9.3 Drug Burden index

The drug burden index (DBI) is considered to have the potential to prevent and/or detect and reverse prescribing of inappropriate drugs (122). Furthermore, DBI could be a tool to predict functional outcomes from drug therapy in older people, providing associations are present (122, 124). The initial DBI-study hypothesized and identified a linear association between a DBI-score and validated function measures in community-dwelling older people between 70 and 79 years (122).

DBI calculates the cumulative (Σ) exposure to drugs with AC and SED properties, adjusting for dose (122, 123). Each prescribed defined DBI-drug included in the calculations are dose-adjusted by applying the hyperbolic DBI-function (see Formula 1.1), adding a value between 0-1 for each DBI drug.

Formula 1.1. *Drug burden index (D=dose of DBI-drug, δ= minimum recommended dose and Σ= sum of scores)*

$$\mathrm{DBI} = \sum \frac{D}{D+\delta}$$

DBI has repeatedly shown associations with adverse outcomes such as falls, mortality, length of hospital stays, delirium and reduced cognitive and physical function in older patients (125). To investigate potential associations between DBI and adverse outcomes for older adults, determining DBI drug-exposure from registry data in patients is increasingly common. Table 1.1 presents an overview of studies where patient exposure to DBI-drugs are estimated based on registry data such as dispensing data, insurance claims or prescription registry data (126-133). All investigate associations between DBI and various outcomes. Participants included in the listed studies were≥65 years, (average age 74-83 years), and most of the participants were female (54-90%). Findings include that increased DBI is associated with reduced quality of life, increased frailty (129), increased length of stay (LOS) and hospital admissions (132) as well as mortality (133) and falls (129, 133). In addition, DBI ≥ 0.5 has been found an independent predictor of increased healthcare costs (127).

Table 1.1. *An overview of studies investigating associations between DBI-exposure calculated from registry data and various outcomes*

Author, Year, Country (ref)	N	Estimation daily DBI-drug exposure	DBI categorization	DBI prevalence (%), Values: mean[a] (SD)	Results
Gemmeke, 2021, Netherland (126)	3454	**Dose:** the last prescription from time = −270 to −180 days from falling.	DBI = 0, DBI > 0 and< 1, DBI ≥ 1.	n.a., Median [Q1–Q3] * 0.51 [0–1,17]	DBI ≥1 and single falling: OR: 1.30 [95% CI: 1.02-1.66] DBI ≥1 and recurrent falling: OR: 1.60 [95%CI: 1.25-2.04].
Gervais,2021, France (127)	1604	**Mean daily dose:** consumption for each reimbursed medication over 6 months/180 days.	DBI <0.5, DBI ≥0.5	n.a., DBI < 0.5[b]: 0.1±0.1 DBI ≥0.5[b]: 0.7±0.4	DBI ≥ 0.5 an independent predictor of increased healthcare costs by 22% (p<0.001).
Ie ,2021, USA (128)	343	Drug provided ≥30 days * >1 during 12 month: (DBI* days' supply)/days between baseline and 12 months.	DBI= 0, low, high burden[c]	49, n.a.[d]	DBI did not predict falls after adjusting for covariates
Byrne, 2019, Ireland (129)	C1 n= 1924 C2 n=1781	**Daily dose**: strength*total quantity dispensed over the 12-months, divided by 365 days to normalize.	DBI = 0, DBI > 0 and < 1 DBI ≥1	C1: 62 C2: 60, C1: 0.63 (SD 0.71) C2: 0.64 (SD 0.70)	**DBI > 0 and < 1 vs none**:** Self-reported falls (OR 1.40, 95% CI 1.08, 1.81), frailty (OR 1.39, 95% CI 1.06, 1.83) reduced QoL (β = − 1.55, 95% CI -2.37, − 0.73). **DBI ≥1 vs none:** Impaired function (ADL OR 1.89, 95% CI 1.25, 2.88; IADL OR 2.97, 95% CI 1.91, 4.61), self-reported falls (OR 1.50, 95%CI 1.03, 2.18), frailty (OR 1.74, 95% CI 1.14, 2.67), reduced QoL (β = − 1.84, 95%CI -3.14, − 0.54). **No significant association** between any DBI exposure and healthcare utilization (hospital admission or ED visits)
Jamieson ,2019, New Zealand (130)	70 553	DBI exposure for each 90-day interval: DBI for each drug multiplied by 90 days.	DBI = 0, DBI >0 and ≤ 1, DBI >1 and ≤ 3 DBI > 3	59, n.a	Higher DBI scores associated with an increased likelihood of hip fractures
Jamieson, 2018, New Zealand (131)	71 856	**Daily dose: d**ividing the 'quantity dispensed' by the 'days' supply'.	DBI = 0, DBI >0 and ≤ 1, DBI >1 and ≤ 3 DBI > 3	62, Median DBI 0.94	DBI groupings were related to falls (p < 0.001). DBI > 3 associated with a 41% increase in falls compared with DBI score of 0 (p < 0.001)
Gnjidic, 2014, Finnish data (132)	AD = 16603 non-AD= 16603	Daily dose: quantity dispensed (strength (mg) *amount dispensed) divided by the time period (120 days).	DBI=0, DBI > 0 and< 1, DBI ≥ 1. Continuous.	AD: 51 non-AD: 33, AD: 0.45 (SD 0.59) non-AD 0.27 (SD 0.49)	**Categorical (IRR):** LOS: AD: DBI 0-1: 1.02 (0.95–1.10), DBI ≥1 = 1.15 (1.05–1.26), LOS: NonAD: DBI 0-1: 1.19 (1.07–1.32) DBI ≥1: 1.63 (1.41–1.88) No.Admissions.: AD: DBI 0-1: 1.18 (1.11–1.26), DBI ≥1:1.41 (1.31–1.52) No.Admissions.: Non-AD: DBI 0-1: 1.33 (1.24–1.43) DBI ≥1: 1.64 (1.49–1.80) **Continuous (IRR):** LOS: AD 1.06 (0.99–1.12), NonAD: 1.35 (1.24–1.46) No.Admissions: AD: 1.22 (1.17–1.27), non-AD: 1.36 (1.28–1.43)
Nishtala, 2014, New Zealand (133)	537 387	Dose (derived from pharm extract files) * number of days dispensed in 365 days/365 days.	DBI=0 DBI>0	43, DBI 0.177 (0.176–0.178) Median 0 (0-4.3)	Falls: 1.561 (1.476–1.651) IRR GP-visits=1.125 (1.121–1.129) IRR Mortality: 1.287 (1.249–1.326) HR

a) *Mean, unless stated otherwise,* ***b)*** *Gervais et al. (2021); for DBI values: calculated average within the DBI categories: DBI < 0.5: (n=879) and DBI ≥0.5: (n=725,* ***c)*** *Cutoff values median values among those higher than 0. DBI-Se: 0.233, DBI-Ach: 0.150,* ***d)*** *Did not report DBI scores, only separated SED/AC scores. DBI-SED score mean (SD): Non-fallers: 0.10 (0.22), Fallers: 0.15 (0.27) DBI-AC score mean (SD), Non fallers: 0.05 (0.15) Fallers: 0.06 (0.13).*

CI= Confidence Interval, ADL= activities of daily living, IAD= Instrumental ADL, AD= Alzheimer Disease, C1= Cohort 1, C2= Cohort 2, GP=general practitioner, LOS= Length of stay, No.Admissions = Number of admissions to hospital, n.a. = not available, IRR= Incidence rate ratio, OR= Odds Ratio, HR= Hazard Ratio, SD= Standard Deviation.

The description of the processes and the reporting of results differ between the listed studies. These studies incorporate DBI as categorical variable in their analysis (126-133). One study use DBI as a dichotomous variable and found that exposure to DBI drugs increased the incidence rate ratio (IRR) for falls, GP-visits, and mortality (133). Gnjidic et al. on the other hand, applied DBI both as a categorical and continuous variable (132). They found that linear increase in DBI increased the IRR for length of hospital stay and number of hospital admissions for patients without Alzheimer's disease (AD), while the latter was found for patients with AD. As a categorical variable, DBI≥1 showed significant increase in IRR with 1.15 for patients with AD. DBI-drugs incorporated in the DBI-calculations in the studies were not standardised, while corresponding minimum doses were extracted from national guidelines. In addition, methods for DBI-drug daily dose estimation vary. Several of the studies calculate an average daily dose based on the amount of dispensed/reimbursed prescribed drugs during the study period divided by number of days in the period (127, 129, 133).

No studies of DBI in a Norwegian population has been conducted. To assess the usefulness of DBI in Norway, high quality studies of potential associations with adverse outcomes are required. This includes identification of drugs with clinically relevant AC/SED properties on the marked in Norway, to get results relevant for Norwegian populations.

1.9.4 Clinical pharmacy services

Individually tailored pharmacist services to optimise drug therapy have been developed to meet drug-related problems prevalent in older patients. Medication reconciliation addresses informational and adherence issues in relation to transitions (94), functions as a tool to identify patient-issues regarding drug therapy, as well as securing correct information as grounds for medication reviews. Medication reviews ensure a thorough assessment of the patients' drug therapy to optimise the quality of drug therapy in use, while patient counselling aims to improve patient knowledge of their drug therapy, to overcome adherence barriers (94). When implemented by pharmacists, medication reconciliation at admission has reduced number of errors (134), medication reviews results in identification and solutions to DRPs (135) and improved drug therapy (136). Improving discharge summaries from hospital decreased transfer errors (137), and pharmacist patient education has resulted in improvement in patient adherence (138). However, conducted reviews of single-standing services did not

find impact on health care utilisation (136, 139, 140). The effect of pharmacist interventions is proposed to be most beneficial in form of multifaceted interventions (141).

1.9.5 The Integrated Medication Management model

Pharmacist clinical services were incorporated in a systematic, stepwise procedure, the integrated medicines management model (IMM) in North Ireland, at the beginning of the century (142). IMM cover defined phases of the patient pathway; admission, hospital stay (monitoring and counselling), and discharge. Contact with primary care physician at discharge was written (per fax). The pharmacist driven IMM-methodology showed promising results in Northern Ireland. When implemented, IMM was shown to shorten length of hospital stay (by 2 days), lower rate of readmission (40.8% vs 49.3%) and, increase time to readmission (by 20 days) (142). Later, it was determined that implementing the IMM-service in clinical practice was beneficial for patients ≥ 18 years, reducing LOS. In addition, it showed trends towards having a positive effect on number of and time to readmissions (143). In Sweden, a similar multifaceted intervention, showed effect on readmissions and visits to the hospital, and reduced health care costs (44). Integrated medicines management have been established in Sweden (43), and has also affected health economic positively (144). In 2009 clinical pharmacists in one part of Norway started to implement IMM procedures (145). Standardisation has primarily been driven by the hospital pharmacies, but the implementation of such services depends on funding allocated to pay for the services. This funding varies greatly; from long-term budget at health trust level, to the individual ward having to find funds in its own budget (94, 146). Consequently, in Norwegian hospitals to date, there is no standardised, integrated clinical pharmacist function/role, and the differences in funding causes variation in what services are provided. Determining and evaluating appropriate work models facilitating interdisciplinary cooperation is of importance, and integrated medicines management models have showed promising results (44, 142, 143). High-quality comparative studies is called for (139-141, 147).

1.10 Knowledge gap and rationale for the studies

In Norway, there is a lack of knowledge concerning effects of drug therapy optimisation approaches on health care utilisation. Nation-specific differences in health care systems decreases the generalisability of studies from other countries to Norwegian settings, hence Norwegian studies are necessary to conduct.

AC/SED drugs are high-risk drugs for older patients. DBI has repeatedly shown associations with short- and long-term adverse outcomes in older patients in non-Norwegian populations (125), but associations with PDI has not been investigated. The goal is to explore whether reducing the AC/SED drug burden can allow older people to live longer at home, which is both financially favourable, and wanted by the older patients, and investigations of correlations between AC/SED drug therapy and PDI in a Norwegian population must be conducted.

Use of registry data enables research on groups of patients either not ethical to include in interventional research or omitted for other reasons (148). Norwegian registry-based studies of prescribing patterns specifically targeting older people as a group exist (74, 149, 150), but studies of older patients' drug therapy merged with specialist health care utilization data is infrequent. There is an unused potential to enlighten associations between older patients' drug use and adverse outcomes across the patient pathway in Norway.

Including health care professions with specific competency on drug therapy, such as clinical pharmacists, is proposed to improve drug therapy optimisation for older patients (92, 93). Although clinical pharmacy is frequently studied internationally, previous studies show consistent shortcomings, e.g., the variability of study design, outcomes, and evaluation, is substantial, limiting general conclusions (136, 138-141, 151). In addition, evaluating the process, e.g., measuring the implementation of the intervention, how it is delivered, and the content of the delivery is important to understand why an intervention succeeds or fails (152, 153).

2 Aims

Overall aim

The overall aim of this thesis is to generate new knowledge of drug therapy optimisation for older patients by exploring the impact of drug burden and investigating different approaches to optimise drug therapy across the patient pathway.

Study specific aims for the four papers in the thesis were

Paper I: To examine if anticholinergic and sedative drug burden at admission to hospital is associated with post-discharge institutionalisation for community dwelling older patients acutely admitted to hospital

Paper II: To describe and implement an interdisciplinary collaboration structure to optimise drug therapy and to improve medication-related communication with primary care for hospitalised older patients- the IMMENSE trial

Paper III: To determine the fidelity of the interdisciplinary collaboration structure, described in Paper II, present rationale for the discrepancies, and display process outcomes of the intervention

Paper IV: To examine and describe the time distribution for the pharmacists running the IMMENSE trial

3 Material and Methods

3.1 Overview

The work in this thesis is a part of an extended project aiming to optimise the use and safety of drug therapy in older patients. The project included i) to increase the knowledge of drug therapy in use and outcomes across the patient pathway for older Norwegian hospitalised patients by obtaining and analysing registry data, ii) to design, implement and investigate an intervention to optimise drug therapy in-hospital in a clinical trial, iii) to investigate and evaluate the implementation of the clinical trial. Generated knowledge will be used to interpret the results from the clinical trial and modify the intervention.

The thesis is based on four papers:

Paper I: Is anticholinergic and sedative drug burden associated with post-discharge institutionalization in community-dwelling patients acutely admitted to hospital? A Norwegian registry-based study

Paper II: Interdisciplinary collaboration across secondary and primary care to improve medication safety in the older patient (IMMENSE study): study protocol for a randomised controlled trial

Paper III: Intervention fidelity and process outcomes of a pharmacist-led interdisciplinary intervention to improve medication safety in older hospitalised patients

Paper IV: Time distribution for pharmacists conducting a randomized controlled trial– an observational time and motion study

We applied quantitative methodological designs. In Paper I we used data from the Norwegian health registries NPR and NorPD in a cross-sectional observational trial. In Paper II-IV we describe, implement, investigate, and evaluate an interdisciplinary pharmacist collaboration model in a randomised controlled trial (RCT). In Paper II, the intervention is described. In Paper III intervention data is collected to quantify the fidelity and process outcomes of the intervention, and, in Paper IV observational data is collected to measure pharmacists time distribution conducting the RCT including the delivery of the intervention (Paper IV).

An overview of the designs, study participants, settings, methods, outcomes, and variables from Papers I-IV are displayed in Table 3.1

Table 3.1. *Overview of designs, populations, settings, methods, outcomes, and variables in Paper I-IV*

Paper	Time frame[a]	Design	Study setting	Population	Methods	Outcome[f]	Variables
I	2013±1 year[b]	Observational, cross sectional	Registry based (NPR/NorPD)	Full: 86 509 Sub-pop[c]: 1715	**Legend**	DBI-drugs at admission	Time of dispensation, prescribed dosage units, number of doses, number of administrations per day
					CCI	Comorbidity measure	Reimbursement codes, ATC codes*
					Directed acyclic graphs	Regression model	Dependent variable: PDI Variables in DAG (and not in final model[g]): Geographic residence, gender, socio economic factors, season
					Scatterplot	Splined exposure Piecewise linearity	Exposure: DBI Outcome (dependent): PDI
					Multiple logistic regression	PDI	Exposure: DBI (splined, number of DBI drugs, dichotomous) Covariates/factors[g]: Age, previous hospital stays, LOS, No. ATC codes, psychiatric disorder, CCI, discharge diagnosis
II	2016-2020	Randomized controlled trial	In-hospital care[d]	n.a.	**Poisson regression[e]** **Survival analysis[e]**	Acute readmissions ED visits	Intervention vs control group. See Paper II for variables
III	2016-2019	Fidelity analysis, intervention delivery	IMMENSE	Intervention 221	**Dose**	Intervention delivery	Intervention steps, causes of deviations from protocol
					Process evaluation	Intervention outcome	Medication discrepancies, MRPs, implementation of suggested solutions
IV	2018	Time and motion; WOMBAT	IMMENSE	Study pharmacists: 2	**Tool development for RCT setting**	Observational tool	n.a.
					CI: resampling, simple bootstrap	Time distribution	Task dimension and category time. Total observation time, interruptions, and multitasking

a) *Comprise period of data extract (I), data collection (III-IV) and data collection plus follow-up (II),* ***b)*** *Index stay in 2013±1 year for each individual,* ***c)*** *sub-population: patients with index stay at geriatric ward,* ***d)*** *University hospital of Northern Norway; one Geriatric & one Internal medicine ward,* ***e)*** *Results from the RCT including follow-up data is expected during 2022, see result presentation, this is the intended analysis for the primary outcome,* ***f)*** *For Paper I and III descriptive statistic of the population was also calculated. In Paper I, we applied Student's t-test to compare means (continuous data; age, CCI, previous hospital stays, number of drugs used, LOS, and DBI mean scores), 95% level of significance,* ***g)*** *variables in the regression model was investigated in the DAG before incorporated in the regression model. ATC= Anatomical Therapeutic Classification, CCI=Charlson comorbidity index, CI: confidence Interval, DAG: directed acyclic graph , DBI=Drug Burden Index, LOS=length of stay, P=Paper, PDI= post-discharge institutionalisation, RCT=randomized controlled trial, WOMBAT= Work Observation Method By Activity Timing.*

3.2 Data sources

3.2.1 National health registries (Paper I)

The rich source of information coming from the Nordic drug dispensing and specialist patient databases can contribute to efficacy and safety research utilising estimations of real-life drug use based on dispensing data (24, 154). Data from The Norwegian Patient Registry was merged with the Norwegian prescription database for exposure and outcome data.

3.2.2 Microsoft access database (Paper II-III)

For the RCT a Microsoft Access® study database was designed for the recording of patient data and process outcomes from the intervention in the RCT. Patient variables were collected consecutively in the RCT (described in Paper II), intervention data was logged by study pharmacists for each step of the intervention (Paper III).

3.2.3 Time and motion observations (Paper IV)

Observations of study pharmacists' time were collected quantitively by a non-participating observer, using a tablet with a predeveloped observational tool.

3.3 Data timeline (Paper I-IV)

Exposure and outcome data related to the patient pathway available from 1 year pre-admission, during hospital stay and 1-year post-discharge is presented in Figure 3.1

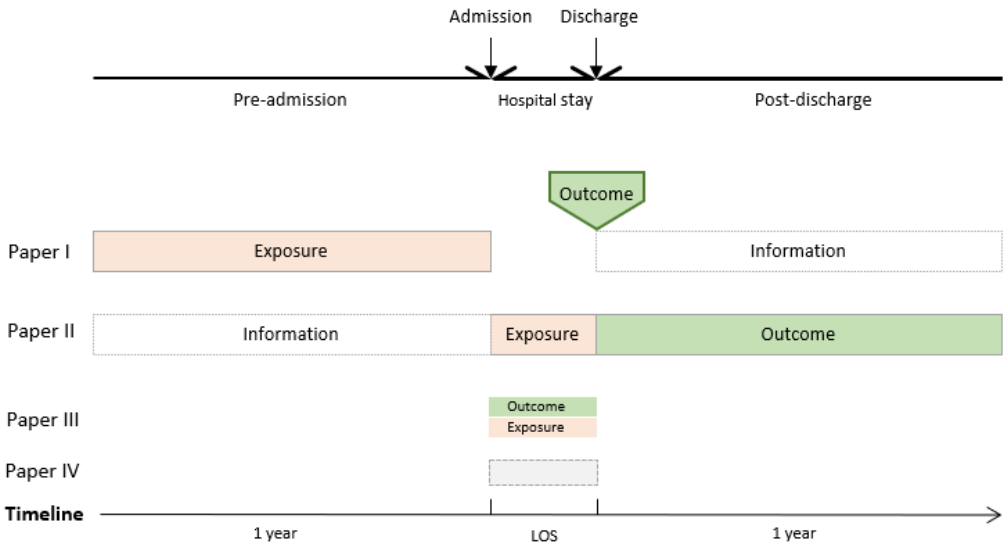


Figure 3.1. Timespan for data availability in Paper I and Paper II-III. **Paper I**: No data from hospital stay besides LOS and main discharge diagnosis. Exposure from registry data. **Paper II**: Exposure= pharmacist intervention. Outcome from registry data. **Paper III**: Fidelity and process outcomes. **Paper IV** measures the time distribution of the pharmacists providing the intervention in-hospital from paper II-III

3.4 Paper I

The inclusion/exclusion criteria determining eligibility of patients is presented in table 3.2.

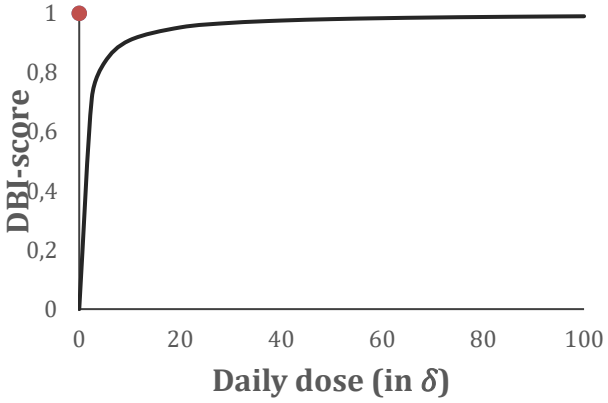
Table 3.2 *Criteria for participation (Paper I)*

INCLUSION CRITERIA	EXCLUSION CRITERIA
Paper I	**Paper I**
≥70 years	Day/outpatient stay
Acutely admitted to hospital	Non-community dwelling
	Non-resident in Norway
	Died during index stay
	Missing main diagnosis
	Duplicates

Establishment of drugs with AC/SED properties for a Norwegian setting (Paper I).
Drugs to include in DBI calculations were not standardised during the development of the index (122). Therefore, the developers recommend nation-based identification of DBI drugs before application of the DBI (123). To identify drugs with AC properties in the Norwegian market I screened the Norwegian Pharmaceutical Product Compendium (NPPC) (66) during spring 2019. NPPC includes descriptions based on the Summary of Product Characteristics for drugs with marketing approval in Norway. A translated and modified (due to differences in languages) list of alternative terms used for anticholinergics from Nishtala et al. (48) was applied, see Appendix 1. The terms were manually applied in the NPPC search engine. Drugs with any term(s) present in the NPCC were listed with the excerpt(s) from the compendium including the term. Based on the excerpts, the drugs were categorized into one of four categories: i) Definitely no AC, ii) ambiguous, iii) definitely some AC, and iv) potent AC properties. Two of the authors from Paper I (KH and KHH) re-assessed the excerpts in group ii) and iii) and agreed on the final list of drugs with AC properties to include in analysis. Drugs with SED properties were defined as ATC-groups for ‘primary sedative’ and ‘sedation as a prominent side effect’ drugs as described by Linjakumpu et al.. (49). To avoid duplicates, drugs with both AC and SED properties were classified as AC, as implemented in the original study (122). Formulations with a systemic route of administration (injections, oral, transdermal and spray for systemic uptake) were included. The final list of drugs included in the calculations is presented in Appendix 2.

Calculation of Drug Burden Index (Paper I)

DBI-drugs actively in use and dose were identified from NoRPD data, by the legend method (155), explained in Paper I. The DBI-score was calculated as the sum (∑) of calculated contributions from each dispensed DBI-drug, and require information on drugs to include, corresponding minimum dose, and daily dose (see formula 1.1 page 19) (122). The DBI-functions hyperbolic contribution of one drug to the index is visualised in Figure 3.2.



D	δ	DBI
0	1	0
0.25 xδ	1	0.20
0.5 xδ	1	0.33
1xδ	1	0.50
2xδ	1	0.67
3xδ	1	0.75
4xδ	1	0.80
5xδ	1	0.83
10xδ	1	0.91
100xδ	1	0.99

Figure 3.2. Input from one DBI-drug as calculated by the DBI. The single drug contribution to DBI is always a value between 0 and 1. D=dose, δ= minimum recommended dose. Here daily dose (D) is based on number of minimum recommended doses (δ).

Hence, one DBI unit (DBI=1) can reflect different scenarios of drugs in use, but never the use on one drug only. As mentioned in Paper I, adding a drug in minimum dose will increase the DBI more than increasing the dose of an existing drug in use by on minimum dose, exemplified in Table 3.3

Table 3.3. *Scores of DBI based on varying input.*

One DBI drug in use:	
Drug A: daily dose = 1 δ → DBI= 0.5	Total DBI= 0.5
Daily dose doubles for one DBI drug:	
Drug A: daily dose = 2 δ → DBI= 0.67	Total DBI=0.67
Instead of doubling the dose, one DBI drug is added, with daily dose=1 δ:	
Drug A: daily dose = 1 δ → DBI= 0.5 and	
Drug B: daily dose = 1 δ → DBI= 0.5	Total DBI= 1.00
Daily dose 10 δ for one DBI drug:	
Drug A: daily dose =10 δ → DBI = 0.91	Total DBI=0.91

We also separated the AC and SED components of the DBI scores to enable investigation of the individual component's potential association with PDI.

Evaluation of linearity of exposure variable DBI vs outcome PDI

The linearity of the exposure variable DBI (x-axis) vs the outcome PDI (y-axis) was investigated in a scatterplot, see figure 3.3.

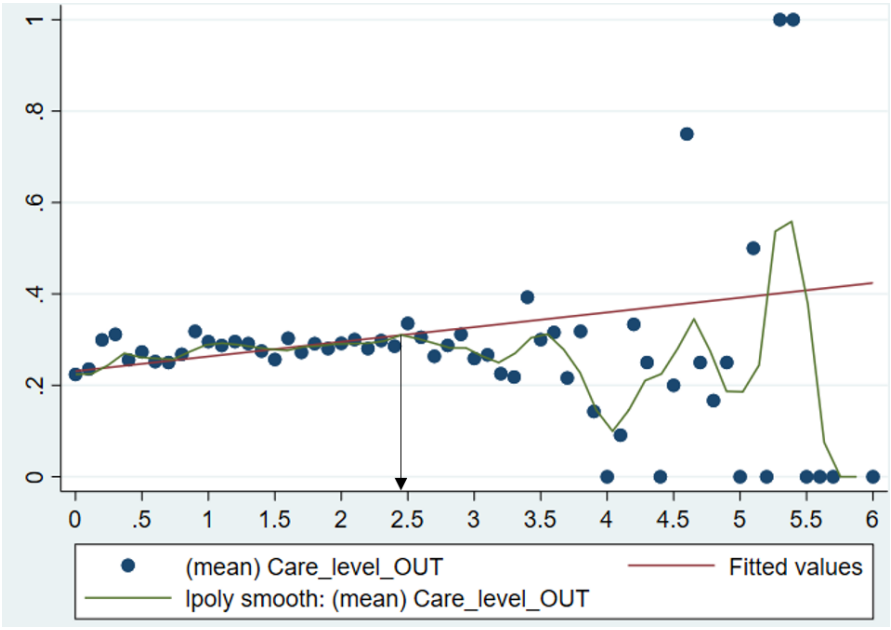


Figure 3.3. The scatterplot of DBI (weighted) (X-axis) and outcome post-discharge institutionalisation (Y-axis). The arrow marks the knot point at DBI=2.45.

By visual inspection of the scatterplot, we observed a shift at DBI 2.45 (see Figure 3.3), identified as a knot point for our analysis. Furthermore, the results are centred for the values <2.45 (n=37371), and, more uncertain for values ≥2.45 (n=1832), increasing when DBI > 3.2. Uncertainty in the higher values most likely a result of lower number of people. Hence, DBI was splined in two linear parts, with knot point at 2.45.

Comorbidities

We used reimbursement codes, i.e., ICD-10 or ICPC-2 from the NorPD to calculate Charlson Comorbidity Index (CCI), in line with the Deyo adaption (156) see Appendix 3, and to construct an additional *mental illness-variable* to include mental disorders not covered by CCI, see Appendix 4. We used reimbursement codes from the year before index stay.

3.5 Paper II-III

The inclusion/exclusion criteria determining eligibility of patients in Paper II and III is presented in table 3.4.

Table 3.4. *Criteria for participation (Paper II-III)*

INCLUSION CRITERIA	EXCLUSION CRITERIA
Paper II-III	**Paper II+III (IMMENSE trial)**
≥70 years	>72 hours since admission to ward
Acutely admitted to hospital	Discharge same day as inclusion
	Inability to understand Norwegian
	Short life expectancy
	Under the care of physician at another ward
	Moved to and discharged from another ward

Intervention elements and procedures (Paper II-III)

The planned RCT and the content of the intervention is thoroughly described in Paper II. An overview of the intervention with descriptions of the services is presented in table 3.5.

Table 3.5. *The intervention structure with descriptions of tools and procedures for each step.*

When	**Step**	**Template/tool/procedure**
At admission	Medication reconciliation **(Step 1)**	a) Adapted IMM medication information retrieval tool: Interview guide addressing drug use, managing of drugs and adherence and documentation of sources of information b) Symptom assessment form: Identify adverse reactions
During hospital stay	Medication review **(Step 2)**	Adapted standardised MedRev template: -Identify DRPs -Present, discuss and find solutions with interdisciplinary team. -Present results for the patient if possible
At discharge	Patient counselling **(Step 3)**	Patients managing their medications: -Updated medication list approved by responsible physician -Counsel session with pharmacist[1,2]
	Medication list for discharge summaries **(Step 4)**	Template of medication list based on hospital procedures and recommendations from the national patient safety program. Basis for the ward physician when preparing the discharge summary.
1-7 days post-discharge	Communication with Primary care **(Step 5)**	a) Day of discharge: Home care service: inform of changes/follow-up[3]. b) Within 7 days: Phone meeting with GP: discussion based on information from discharge summary[3].

1) In addition to the standard discharge meeting between patient and physician. 2) Conducted for patients managing their drug therapy, 3) Not relevant for patients with no change in medications/no identified need for follow-up. GP= General Practitioner

Intervention steps 1 and 2 incorporate thorough, structured procedures to identify and resolve drug-related problems. All intervention steps address factors affecting implementation of drug therapy by increasing patient knowledge and communication between care levels. Step 5 specifically focus on monitoring and transition. We screened all admitted patients and invited eligible patients to take part in the trial. Step 1-4 are equal to the original IMM-intervention (142), while adding step 5 increase focus on transitional challenges.

Intervention delivery (Paper II-III)

During the inclusion phase, a total of six pharmacists were involved collecting data at the two study wards. The study pharmacists all held a master's degree in pharmacy and had received training in the IMM methodology. The pharmacists performed medication reconciliation directly after inclusion for intervention patients. A thorough medication review followed. The pharmacists were not authorized to perform changes in drug therapy without physician consent. The study pharmacists did not take part in ward rounds, DRPs and suggested solutions were discussed during pre-round meetings. Participants in the teams were physicians with or without geriatric specialty, nurses, and therapists. The physician in charge would ultimately decide whether to implement suggestions from pharmacists. If decisions were pending, improvised discussions could be initiated, depending on the urgency of the situation. Drug-related problems, suggested solutions, and outcomes from discussions would be recorded in the electronic patient journal by the study pharmacists. Further, the pharmacists would ensure updated discharge information, to patient and next level of care. Pharmacist resource allocation differed between the study-wards. *Study ward A*: At least one pharmacist was present at the ward all weekdays. Inclusion was conducted if eligible patients were at the ward. *Study ward B*: A 50% pharmacist position was available for the RCT. Inclusion followed the schedule for pharmacist presence in the ward.

Intervention fidelity and process outcomes (Paper III)

Intervention fidelity measures the implementation of the intervention which is one aspect of process evaluation (153). Data registered during the IMMENSE supply information covering one fidelity approach, the "dose"(157, 158). "Dose" is characterized as "the amount of an intervention received by the participants" and "completeness and dosage of implementation" (157). The dose was addressed by using the information recorded in the study database. The overall completeness of the intervention and number of participants receiving each step and combinations are described in Paper III, together with process outcomes.

3.6 Paper IV

Study participants

Study pharmacists delivering the intervention described in Paper II. We observed the pharmacists at study ward A since pharmacists were present all weekdays. Study ward A had two pharmacists conducting the RCT and delivering the intervention during the study period.

Development of observational tool

The Work Observation By Activity Timing (WOMBAT) method's multi-dimensional framework can be designed to measure most settings (159, 160). Still, no observational tool for a RCT setting existed, and required development. We applied the four dimensions *what, who, where and how*. Overall categories were determined by deriving RCT and Non-RCT groups from the aim, while social/break-group was added as a separate category. Clinical communication is often a separate task in WOMBAT-studies (159), however, this did not meet the aim of this study. Non-verbal and verbal time within each task was imperative to measure without losing task affiliation. The "how" dimension categories "face-to-face" and "phone" were used to define verbal communication, which has not been done previously. The observational tool-design was piloted repeatedly in the setting by two of the authors from Paper IV (KH and EL) before initiating the data collection.

Observations

We conducted a time and motion study applying WOMBAT methodology (159) to assess time distribution for the two clinical pharmacists then active at Study ward A in the RCT. The observation period covered 8 weeks in late fall 2018 (year three of the RCT). A researcher independent from the RCT conducted the observations. The observed pharmacists knew the observation schedule, mainly to ensure their presence in the ward at times of observation.

Task time calculations

The data recorded via the tablet was uploaded to the web application, then downloaded as a CSV (comma-separated value) to Statistical Analysis Software (SAS). The total observational time is calculated by subtracting start time from stop time for each session, and then summing up all sessions. Summary measures of time proportion of each task were performed. When two or more tasks were recorded concurrently (multitasking), time passed was recorded once for each task, thus the task time exceeded the time observed. Interruptions are analysed as number of interruptions and rate of interruptions, either of overall time, or within a category/task.

3.7 Statistical analysis (Paper I&IV)

Paper I

For variables and outcome, see table 3.1. The variables were investigated in a correlation matrix. A multiple logistic regression model was built with DBI as a splined, continuous, exposure variable. Furthermore, DBI was replaced with the other measurements of AC/SED drug burden in the same model. Associations with outcomes were calculated as odds ratios (OR) with 95% CI. P values <0.05 were considered statistically significant.

Paper IV

To avoid the possibility of generating corresponding 95% confidence intervals (CI) outside the possible range (below zero) for time, a bootstrap approach with resampling was used as described in the analysis guide (161) and in Paper IV.

3.8 Computer software

IBM® SPSS Statistics v26 was the main software for management of data, descriptive statistics, and basic calculations for Paper I, II and III, while most tables and figures visualizing data and/or results was constructed in Microsoft® Excel 2019.

For study I, the logistic regression model was built and analysed in STATA MP16.0, while the basis of the model incorporated was designed as a Directed acyclic graph (DAG) using the free online software DAGitty (162).

In study IV, we used WOMBAT software on a tablet (Samsung Galaxy Tab S2) to record activity, while the data, as a comma-separated value (CSV) file (generated from the WOMBAT software), was downloaded to and analysed with the Statistical Analysis Software system for Windows, v 9.

3.9 Ethical aspects

Paper I

The study was approved by the regional ethics committee (REK-reference: 2014/2182, Project number 25995) and the Norwegian Data Protection Authority.

Paper II and III

The IMMENSE study has approval for data collection and data storage by the Norwegian Data Protection Authority, Regional Committee for Health Research Ethics has approved identification of patients at the clinical departments. The RCT was conducted in compliance with the ethical principles from Declaration of Helsinki. To be included in the study, patients (or next of kin if patient unable to consent) have provided written consent.

One ethical consideration involved potential consequences of reduced consent competence. Written informed consent by patient, or next of kin if patient is not consent competent, is the common approach. However, this is not always an either/or situation. Patients in early phase dementia can be able to consent regarding health care decisions or daily activities, but the concept of trial participation can be too complicated. The determination of a patients' ability to consent had no standardised procedure in the wards. For patients where there was uncertainty regarding the consent competence, the study pharmacists informed both patient and next of kin, for them to decide together about participation. We then collected written consent. In addition, the intervention was seen as beneficial for the patients. No follow-up was required from the patient's perspective, except receiving phone calls for quality-of-life measurements. On the other hand, patients in the control group missed an intervention believed to be beneficial.

Paper IV

During observations we did not record patient sensitive information. In accordance with Norwegian guidelines, no ethical approval was necessary (The Regional committee for medical and health research ethics, Norway, reference number 2017/685). However, the two study pharmacists consented to being observed. Other health care personnel at the ward were also informed of the study.

Ethical challenges for the researcher as a health care professional

An ethical dilemma experienced during the study period was regarding control patients. Control patients did not receive any pharmacist services. Study pharmacists received many

requests regarding advice concerning control patients, which they had to deny answering. However, requests decreased over time. This conflicts with the study pharmacist role as a health care professional, where your intention not only is to help the patients but to improve collaboration to improve the drug therapy optimisation process.

4 Results

4.1 Patient populations

A comparison of selected data on characteristics and drug therapy is presented for the study population in Paper I and the per protocol group from the RCT in Paper III. See Table 4.1.

Table 4.1. *Comparison of selected population characteristics from Paper I and III*

	Paper I	Paper III
	Study population (N= 86509)	**Per protocol group (n=221)**
Age **mean (SD)**	81.5 (7.0)	83.4 (6.3)
Female **%**	56.6	63.3
Number of drugs at admission[a]	7.1 (SD 4.09)	6 (IQ Range 4-9) [b]
LOS **(range)**	Mean 5.3 (1-132)	Median 5 (0-48)
Discharged to institution	24.6%	n.a.

a) For Paper I: Mean number of ATC codes dispensed per patient 120 days before admission (SD), for Paper II: Median number of drugs before medication reconciliation b) Medications regularly in use. In addition, patients used median 2 (IQR 0-3) as needed medications. GER=geriatric, SD= standard deviation, LOS=Length of stay

The patient populations in the two studies are similar with regards to drug use. The per protocol group in Paper III is older than the full study population in Paper I. In addition, the populations differs in female representation, with 56.6% and 63.3% in the Study population (Paper I) and Per protocol group (Paper III) respectively.

4.2 Paper I

Paper I report the prevalence of patients exposed to AC/SED drug burden, DBI scores and investigates the association between AC/SED drug burden and PDI for older hospitalised patients. Selected patient characteristics are summarized in Table 4.1.

The prevalence of patients exposed to AC/SED drugs was 45.4%, and average DBI was 0.48 (range 0-6.04, SD 0.68). The association between DBI-score and PDI was OR 1.11 (1.07-1.15 95% CI) for DBI <2.45 and OR 1.08 (1.04-1.13 95% CI) for DBI ≥2.45 for each one-unit raise of DBI. DBI scores for the AC component alone showed a stronger association with OR 1.23 (95% CI (1.15, 1.31). Substituting DBI with number of DBI drugs in the logistic regression model was more sensitive than DBI, with OR of 1.07 for PDI per DBI-drug compared to 1.09 per unit DBI, while number of AC drugs showed the strongest association with PDI of all the alternatives investigated with OR 1.13 (1.13 (95% CI 1.08, 1.17) per AC drug. These effects were not found in the geriatric subgroup, where ORs for AC exposure (DBI AC component and number of AC drugs) were closer to one, although not statistically significant due to population size. The number of ATC codes in use, adjusted for in the regression model, had no association with PDI with an OR 0.99 (0.98-0.99 95% CI) in the study population.

Conclusion: We identified an association between AC/SED-exposure and post-discharge institutionalisation. DBI scores showed the weakest association, number of DBI drugs had a slightly stronger association with PDI compared to DBI-scores, while counting AC drugs was most sensitive for the outcome. Number of ATC-codes on the other hand had no association with PDI in the study population. In summary, an approach to reduce the risk of PDI could be to decrease number of AC-drugs, which is more sensitive, and easier to apply than reducing DBI-scores.

4.3 Paper II

Paper II presents the protocol for the IMMENSE trial describing the intervention, outcomes, data sources and analysis plan of the trial. The RCT was conducted to investigate effects from integrated medicines management, provided by pharmacists, on health care utilisation outcomes. The intervention address challenges and barriers of drug therapy optimisation.

The recruitment of participants lasted over three years: September 2016 - December 2019. Follow-up was completed in December 2020. The main study is to be published in 2022.

4.4 Paper III

Planning and conducting the implementation of the RCT, including development of procedures, technical support systems and databases for logging intervention/study data, as well as performing the intervention and collecting data, was a major part of the doctoral work leading up to this thesis. However, the inclusion phase was estimated to take 18 months, but took 40 months. For my thesis, it was therefore decided to include the fidelity and process outcomes for the per protocol intervention group, as presented in Paper III.

Paper III presents the fidelity and process outcomes from the IMMENSE trial for the per protocol group. Selected characteristics of the per protocol group is presented in Table 4.1

Fidelity: Overall fidelity was 54.8%, while 34.8% of the patients missed one step. All individual steps had a fidelity of at least 80%. Medication reconciliation (step 1) and medication review (step 2) was conducted for all patients. Patient counselling (step 4) was limited by the number of patients (49 patients, 22.2%) managing their own medications. Four of five eligible patients received the GP intervention (step 5a), half of the patients received the step according to protocol timeline. Pharmacist resources and primary care physicians' accessibility were recorded as main reasons for protocol violations.

Process outcomes: The pharmacists identified medication discrepancies and medication related problems for 71.9% and 94.6% of the patients, respectively. Suggested solutions for identified DRPs were solved in hospital as recommended by the study pharmacists in 67.2 % of the instances, while 22.1% was communicated to primary care for follow-up.

Conclusion: Most per-protocol patients **(**54.8%) received every step of the intervention. All patients received the first two steps which ensured identification and solutions to many discrepancies and drug-related problems. The intervention addressing transition out (step 3-5) was more challenging to deliver. In summary, the pharmacist intervention successfully identified and addressed discrepancies and drug-related problems for patients during hospital stay, but fidelity issues may have compromised the full potential of the intervention, particularly regarding the transition out.

4.5 Paper IV

Paper IV presents time distribution for the clinical pharmacists running the IMMENSE trial (Paper II).

Of the 110.2 total task time hours (for both study pharmacists combined), 85.4% was observed as RCT tasks. The pharmacists spent 59% of the RCT time on the intervention (55.3 hours), further, when the pharmacists performed the intervention, 63 % of the intervention time was allocated to medication reviews (step 2 of the intervention). The time spent clinically on each intervention patient during the observations was substantial, estimated to >3.5 hours/intervention patient. When performing intervention tasks, the pharmacists communicated verbally 14% of the time.

Conclusion: For economic analysis, the time spent on administrative tasks should be omitted evaluating the intervention. Moreover, excessive time was devoted to performing the intervention per patient, and communication with other health care personnel was lower than expected. In summary, the potential differences between the RCT-setting observed and a clinical setting might hamper the transferability of the intervention to real life practice.

4.6 The patient pathway and findings from the studies

The main findings are present in different steps of the patient pathway. A presentation in connection with the patient pathway follows (Figure 4.1):

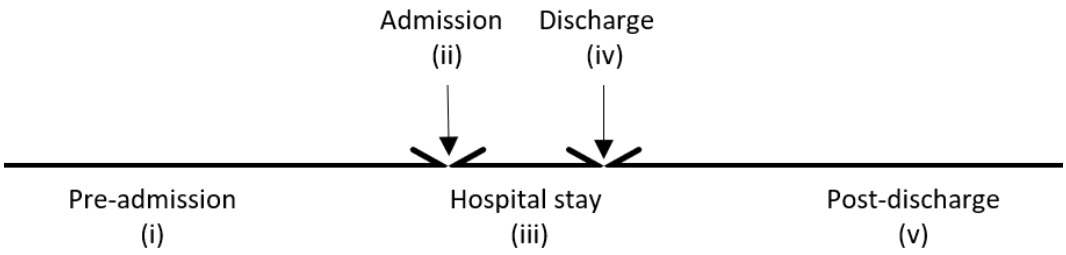


Figure 4.1. The steps in the patient pathway labelled. Findings from the studies in connection with the steps is presented below.

Pre-admission (primary care) (i): Number drugs in use in the period (120 days) before hospitalisation was high (7.11, SD 4.09) (Paper I).

Admission (ii): Drug therapy was prevalent and drug burden high (Paper I&III). Medication discrepancies in the admission phase were commonly identified (for 71.9% of the patients, Median 1) (Paper III).

Hospital stay (iii): Medication discrepancies (71.9%) were proposed solved by the study pharmacists and implemented for 66.8% of the suggestions (Paper III). The pharmacist intervention resulted in identification of 4 (median) drug related problems and high degree of implementation of suggested solutions (67.2%) (Paper II+ III). Time to perform the intervention per patients was high (>3.5 hours observed time) (Paper IV).

Discharge (iv): Few patients (112) received patient counselling, further, only 50% of the patient receiving counselling got an updated medication list. Structured medication list for discharge summaries was achieved for 177 of the 221 patients (Paper III).

Post-discharge (primary care) (v): PDI was common for hospitalised patients. AC/SED drug burden showed a significant association with PDI for all alternatives investigated, while number of AC drugs showed the strongest association with PDI with OR 1.13 per AC drug. Total number of drugs in use before or at admission showed no association with the outcome (Paper I). Contact with primary care physician was achieved for four of five patients, 50% within the per protocol 7 days (Paper III).

5 Discussion of results

5.1 Summary of findings

This thesis has generated new knowledge of drug therapy optimisation by exploring the impact of drug burden for older hospitalised patients and investigating approaches to optimise drug therapy across the patient pathway. Older Norwegian patients have a high drug burden before and at acute admission to hospital (Paper I&III), and AC/SED drug burden at admission was significantly associated with PDI. The number of AC drugs were most sensitive for PDI, while the DBI was least sensitive, and the most challenging to apply (Paper I). During hospitalisation, clinical pharmacist contributed to drug therapy optimisation by identifying and solving medication discrepancies and DRPs for the older patients (Paper III). Benefits of the pharmacist intervention included the high fidelity at admission, identification of DRPs and implementation of solutions, and that the pharmacists advanced communication of drug therapy across the patient pathway (Paper II-III). Drawbacks include that the intervention steps at discharge had lower fidelity, and that the time used to deliver the intervention per patient was high (Paper III-IV).

5.2 Identifying and assessing drug burden in older patients (Paper I-III)

Receiving drug therapy is experienced burdensome by patients, even if the drug therapy gives positive impact on disease. When number of drugs in use and complexity of the drug therapy regimen increase, experienced drug burden increases (163). In our populations, drug use was extensive before hospital admission. The patients used 6 (median) - 7.1 drugs (mean) (Paper I&III), some even as much as 35 (Paper I). From Paper III, we learned that a substantial proportion of elderly did not manage their medications, probably because of cognitive issues (patient not capable), or complexity of the drug therapy. It may also be a sign that medications are burdensome to deal with, which is consistent with findings by Krska et al. who identified that patients with help managing medicines and frequent drug dosing regimens reported high drug burden (164). Therefore, in older patients, it is important that the patient experiences are considered when assessing the burden of drug therapy.

Polypharmacy does not distinguish between drugs that improve the patient's health and/or quality of life, and drugs with potential to cause harm. Thus, the number of drugs in use may not be the best measure when assessing the appropriateness of a drug regimen (165). We have illustrated this in Paper I, when separating drugs in the form of AC/SED drugs or not

AC/SED drugs. We identified a significant association between AC/SED drugs and the outcome PDI, where AC drugs showed the strongest association. No significant association was observed for the total number of drugs in use and PDI in the full study population, while it even showed a significant, but small decrease in risk with OR of 0.95 (95% CI 0.92-0.99) in the geriatric subgroup in our model (see Supplementary 3 Paper 1). This supports the argument by Davies et al. that specific single drugs or drug classes can be of greater importance when identifying inappropriate use of drugs than polypharmacy alone (166). In addition, by investigating implications of drug therapy on an individual drug level (Paper III), all aspects of drug-related problems were identified; over-, under, -and mis prescribing, as well as adverse drug reactions. We also learned that certain drugs were more often involved than others. For example, zopiclone, a SED drug, was the drug most frequently causing DRPs in Paper III. In conclusion, knowledge of specific high risk drugs is important when evaluating and optimising drug therapy, while polypharmacy in itself should not be seen as a problem when adressing the patients drug burden.

We established that high-risk drugs were commonly prescribed to older Norwegian community dwelling patients admitted to hospital, DBI drugs had prevalence 45.4% and 52.5% in the study population and geriatric subgroup respectively (Paper I). One reason for the high prevalence can simply be that recognizing drugs with AC/SED properties can be challenging. By our work in Paper I, we experienced that the use of different terminology and vague descriptions in the NPPC made the identification of AC properties troublesome and time consuming. A 2016 survey identified the NPPC as most commonly used informational tool regarding medicinal products among physicians in Norway, it was also rated among the most reliable sources of information (167). Hence, the inconsistent use of terminology makes the information less accessible, potentially contributing to prescribing of inappropriate drugs. Recently, a Norwegian pharmacist-initiated initiative to provide an AC drug list (168) generated an immediate response a suggesting changes (169). The primary suggestions concerned omission of drugs in the proposed list, and questions concerning the terminology used, which is in line with our experience. Previous findings have also determined that prescribers have incomplete knowledge of drugs with AC properties, and the risks of prescribing them to older patients (170, 171). Hence, consistent, recognizable, and easily accessible information of high-risk drugs can be a crucial step towards reducing drug burden in older patients.

From the number of drugs in use among older hospitalised patients shown in Paper I&III, and changes made during hospitalisation shown in Paper III, we have learned that older patients across the patient pathway in the Norwegian health care system are actively treated with drug therapy. A reason for this can be that older patients show concerns about removing drugs. An active approach to treatment is valued by patients and next of kin (172). This, however, is not necessarily consistent with health care decision guidelines in Norway. Although age is not a legal criterion for decisions regarding right to treatment, loss/gain of years of life is essential for valuing the potential outcome (173). On the other hand, physicians have reported that pressure from patients and next of kin to continue treatment may influence decisions (174). Thus, pharmacist involvement drug therapy optimisation in interdisciplinary teams could be a support for the physician, and beneficial for patients, supporting the presence of pharmacists in interdisciplinary teams.

5.3 Pharmacists in drug therapy optimisation for hospitalised older patients (Paper II-IV)

The findings in Paper III show that the pharmacist affect aspects of drug therapy optimisation. All per protocol patients received medication reconciliation and medication reviews. The pharmacists identified discrepancies in medication lists for >70 percent of the patients (median 1) and identified DRPs for almost 95% of the patients (median 4). In addition, they contribute to solving DRPs, and facilitate information flow across the patient pathway.

The amount of DRPs (median 4) (Paper III) differed from three recent Scandinavian studies implementing similar pharmacist interventions. We identified considerable fewer DRPs compared to a recent Norwegian study, the OPERA trial, which identified a median of 19 DRPs per patient (175), but more than Kempen et al. which found a mean of 2 DRPs per review (176). Ravn Nielsen et al. did not specify the actual numbers of DRPs but suggested approximately one intervention per patient (177). Reasons for these differences are not clear. Inclusion criteria, population characteristics and drug use can affect the presence of DRPs, while variations in pharmacist competence, skills, and experience would affect the identification of DRPs. Furthermore, differences in definitons of DRPs matter, but definitions and clinical significance of findings are often not reported. To fully understand the impact of an intervention, knowledge of clinical significance of the DRPs reported is essential to explain results or lack of results from the trials, in addition to enable comparison. Nevertheless, the prevalence of DRPs signals a considerable potential for improvement, hence, interventions to optimise drug therapy is highly relevant for this population.

One indicator of clinical significance of DRPs can be the acceptance rates of suggested solutions. Acceptance rates can be affected negatively by patient's risk factors, many DRPs and polypharmacy (178), factors highly present in our population (Paper III). The patients were old, drug burden was extensive, and number of DRPs were four (median). Still, the acceptance rate in-hospital in Paper III (67%) was not only in the higher end compared to similar interventions, reporting acceptance rates between 57% and 72% (44, 175-177, 179), additional DRPs were also suggested solved in primary care. Reasons for the high acceptance rate is probably multifaceted. Physicians value pharmacist contributions (180, 181), thus, the pharmacist presence and direct communication with physicians in charge likely affected the acceptance rate positively, which is supported by previous findings (182). More importantly, the high acceptance rate might reflect clinical significance of proposed DRPs and suggested solutions. This is in line with findings from Blix et al., that clinical significance of the DRPs positively affect acceptance rates (182). However, to increase the understanding of the total pharmacist contribution, an investigation of the DRPs not accepted, in addition to the DRPS solved, should also be conducted. Nevertheless, the high rate of acceptance suggests that the pharmacists have contributed to clinically relevant optimisation for the patients.

During admission, all patients received medication reconciliation (Paper III), while the steps in connection with the transition phase from hospital was more challenging to deliver. The pharmacist intervention designed (Paper II) includes continuation of the results from the in-hospital intervention to primary care. Information was delivered by dissemination of lists og drug therapy in use in discharge letters, and direct communication with primary care. This is more extensive than Lea et al., who were "true" to the original IMM model and "stopped" the intervention with written communication at discharge (175). In contrast Ravn-Nielsen et al. (Denmark), had hospital pharmacists perform a comprehensive follow-up post-discharge. Their intervention comprised follow up with primary health care GPs, pharmacies, and care givers, they also included patient follow-up based on the patient's needs, on at least two occasions (177). Lea et al. found an effect on long term deaths, while Ravn-Nielsen et al. found an effect on readmissions and ED visits. It is difficult to explain the potential impact of different priorities in the discharge phase. However, we believe continuation of drug therapy changes in hospital was facilitated by the pharmacist's involvement at discharge in our intervention (Paper II). GPs report positive attitudes towards pharmacists' contributions, but can be reluctant to the pharmacist involvement, especially if they come with suggestions without knowing the whole clinical picture for the patient (183). The latter can be the case for

hospitalised patients, information of prior clinical decisions made by the GPs may not be known. However, this potential issue was met by direct communication, the pharmacists initiated conversations regarding changes and suggested monitoring to primary care (Paper II-III), which is an approach supported by previous studies(182). The direct communication with primary care most likely increases knowledge of changes made in-hospital, thus facilitating the continuity aspect of drug therapy optimisation.

Medication lists were often not approved by physician in time for the pharmacists' patient counselling before discharge, as a result only 55% of the patients received a written medication list during counsel sessions (Paper III). A potential explanation could be that the pharmacist role was not fully understood and/or accepted in the ward teams. Pharmacists in interdisciplinary teams are relatively new in the Norwegian hospital setting (94), and the intervention (Paper II) was implemented without taking potential conflict with established roles into consideration. Hence, the health care system might not have adapted to the study pharmacists' responsibilities and contributions, and vice versa. This is in line with Kempen et al.'s findings, that the "pharmacist role compatibility with hospital practice is challenging, and roles and responsibilities are unclear", when assessing a similar intervention in Sweden (184). They identified barriers such as lack of team participation, unclear pharmacist role and organisational lack of adaption to pharmacists. To determine roles and responsibilities corresponds with principles for interdisciplinary collaboration (99). A mutual understanding of roles and responsibilities between the pharmacists and the team could contribute to better execution of role responsibilities, with benefits for the patients.

On the other hand, conflicting roles may also have impacted the pharmacist contribution. In Paper IV we demonstrated that 40% of the pharmacists RCT time was spent conducting study administrative tasks alongside the intervention. The RCT also implied keeping distance to control patients. In addition, two the study pharmacists had to combine two roles, namely being clinical pharmacists as part of the interdisciplinary team and being a researcher and/or a study pharmacist. This most likely affected full integration in the interdisciplinary teams. Furthermore, since our study went on for 40 months (Paper II), the study pharmacist had to get to know new ward physicians regularly. One consequence was that new physicians needed information and priming into the contributions from the study pharmacists. Consequently, the teamwork would be hampered in the beginning since the parties had to build relationships and get to know each other, and interpersonal work relationships are considered a facilitator for

interventions (184). Lack of integration of collaborating members can decrease the effects of collaboration and reduce the effect of interventions performed (182, 185), which should be taken into consideration when evaluating the analysis of the main endpoints of the trial.

5.4 Evaluation of the integrated medicines management model (Paper II-IV)

We demonstrated an overall fidelity of 54.8%, while single step delivery was between 80-100%. All per protocol patients received medication reconciliation and medication review, while medication lists at discharge and calls to GP were just above 80% (Paper III). The pharmacist spend >3.5 hours on average on the intervention per patient during the observations (Paper III).

The pharmacists spent much time providing the intervention to each patient. The observed intervention time per patient at an average >3.5 hours, raises feasibility issues with the intervention. Real intervention time was presumably even higher since the observations were conducted only half of the day during the study period (Paper IV). This was remarkably high compared to similar trials reporting between 0.5-1 hours per patient (144, 179, 186), but it is more in line with Gillespie et al., who reported a mean of 2 hours and 20 minutes per patient. Interestingly, Gillespie's population was the oldest old (included patients >80 years), and they reduced number of visits to hospital and drug-related readmission for the intervention patients (44). Time spent on the intervention likely reflects the complexity of the intervention, since there were multiple steps to perform. Higher number of steps would require more time. In addition, the procedure for each step can contribute to complexity. However, the slow inclusion rate allowed for the pharmacists to distribute time to tasks of interest or where needed/wanted. Given that 60% of the observed time was spent on medication reviews, it is likely that the complexity connected to patient/drug factors increased the intervention time used per patient in this trial in addition to the complexity of the intervention itself.

We have demonstrated that there were steps in the designed intervention with limited applicability in the population studied. For example, when only 22% of the patients in Paper III managed their own medications at discharge, patient counselling was less relevant for almost 4 of 5 patients. Patient involvement is considered essential to enable shared decision making (187) and ongoing contact with pharmacists affect adherence positively (138, 188). Our focus on patient involvement as part of transitional care should be upheld. This step is

important for those eligible, but other means to improve transitional care for non-eligible patients is important for most of the patients in our population. For these patients, contact with care givers in primary care may be essential, which was a major step in the Ravn-Nielsen trial (177). This implicates there are aspects to consider for future approaches to drug therapy optimisation for this patient group and highlights essential considerations for multistep interventions. The intervention steps should be adapted to population characteristics and needs, rather than being a "one size fits all".

We demonstrated that single steps had high fidelity (>80%, Paper III), but that delivering the whole intervention to the patients in the ward was more challenging, with an overall fidelity of 57%. Implementing all steps as a single-ward intervention may not be optimal. Medication reconciliation is one example. Although the intervention was successful in delivering medication reconciliation to all intervention patients, the structure can be improved. Medication reconciliations are considered an important drug safety intervention in Norwegian hospitals, often performed at admission (189). In the trial (Paper II-III), the patients arrived at the ward with a list of drug therapy, which the pharmacist "reconciled". This can increase the risk of two list documented for the patients during the same stay, and it generates more resource use since two parties obtain lists separately. The goal should be to provide a correct drug therapy list at the first point of contact in the hospital system instead of medication reconciliations at the wards to "control" the job already done. Having pharmacists dedicated to performing medication reconciliation in emergency departments could decrease the load for physicians and be beneficial for the patients. This is supported by a Norwegian study which observed that obtaining and documenting patients' drug lists was only one of many tasks for the emergency department physicians (190). Integrating pharmacists into emergency department teams his is currently investigated in Norwegian hospitals (191). This illustrates that intervention steps can be performed in separate locations, and that interventions to optimise drug therapy might contribute more if they are patient pathway-based, not ward-based. Finding the most appropriate settings across the patient pathway for the separate intervention steps can be crucial both to optimise resource allocation, and to enhance drug therapy optimisation across the patient pathway.

5.5 Implications for drug therapy optimisation across the patient pathway (Paper I-IV)

Findings across the patient pathway include: Pre-hospital (primary care): drug burden is high before hospitalisation, number of drugs in use was median 6 (Paper III) and mean 7 (Paper I), and 45.4% of the full population used one or more AC/SED drugs, with a mean DBI of 0.48 (Paper I). At admission: discrepancies were identified in 72 % of obtained lists, which originate from primary care and/or transition phase between care levels (Paper III). During hospital stay: inappropriate prescribing was prevalent with DRPs identified for 94.6% of the patients (median 4), resulting from prescribing in primary care and in hospital (Paper III), LOS was mean 5 days (Paper I), and median 5.1 (Paper III). At discharge: only 22% managed their drugs at discharge, and most patients were not eligible for patient counselling (Paper III), and primary care team-involvement is important. Post-discharge (primary care): Primary care physicians were difficult to contact within the 7 days per protocol definition. Drug therapy prior to hospitalisation was associated with post discharge institutionalisation.

Most of the identified challenge/problems in this thesis were generated from primary care. We have showed that extensive drug use occurs in primary care and that the drug burden is high (Paper I&III). One obvious reason for this is that the older patients spend most time in primary care. LOS was mean 5 days in Paper I, and median 5.1 days in Paper III. This is comparable to the Norwegian national mean of 4.6 days for 70-90 year olds with inpatient hospital stays in 2021, who also had 1.8 hospital stays a year (27). Furthermore, lack of knowledge and training among prescribers in primary care can explain the magnitude of problems identified. This is supported by a recent Norwegian study, where training programs for GPs were highly effective in reducing inappropriate prescribing in older patients, with impact on the quality of prescribing as well as frequency of medication reviews (192). Increased competence in primary care can improve the quality of drug therapy, and could even affect outcomes from hospital, as AC/SED drug use, in primary care, was associated with PDI (Paper I). One measure can be to introduce pharmacists into Norwegian primary care teams, dedicated to follow up on drug therapy. This could reduce the workload for GPs, as stated in in a 2019 review (193), and could delay hospitalisation, as concluded by Nymberg et al. (194). Nevertheless, our findings are noticeable signs that measures are needed in primary care to improve the quality of drug treatment for elderly patients across the patient pathway.

Asking whether the hospital stay is the setting where we can achieve the best results in drug therapy optimisation is timely. Advantages of intervening in-hospital include that hospitals have established interdisciplinary teamwork, which is also pointed out by Gillespie at al. (44). On the other hand, the GP is absent in this setting. The GP is legally responsible for coordinating drug treatment, and conducting medication reviews for their patients according to Norwegian regulations (195), and probably holds the most extensive and updated drug therapy history. Moreover, the average hospital stay is most often of a short duration as pointed out earlier, which makes it difficult to evaluate changes made. Hence, evaluation of changes made, and follow-up is often continued into primary care. We showed this in Paper III, where we communicated 22.9% of suggested solutions to DRPs, together with changes and follow-up for 89.5% of the patients, to primary care. Furthermore, previous studies have showed that extensive changes in drug therapy often occur in the first phase after hospitalisation (196), which emphasize the need for evaluation post discharge. The intervention at a single point in the patient pathway may not be optimal from a long-term perspective. Nevertheless, delivering the intervention in-hospital most likely increased the quality of drug therapy and facilitated information flow during the hospitalisation (Paper II-III).

New symptoms and/or acute events/exacerbations are presumably present when patients are acutely admitted to hospital, and an acute hospitalisation can be a less appropriate phase to re-evaluate drug regimen and implement major changes. There are several reasons for that: Firstly, treating cause of admission should be a priority. For patients with a drug-related admission to hospital, the hospital stay can be a crucial moment, and we have demonstrated that pharmacists contribute to reveal DRPs for acutely admitted older patients in-hospital (Paper III). However, an active approach to treatment does not necessarily reduce the drug burden, as demonstrated by Johansen et al., who found that neither the number of drugs nor the number of potentially inappropriate drugs were reduced in older patients admitted to Norwegian geriatric wards (197). Secondly, implementing many changes over a brief period complicates the evaluation of effects of each change. Introducing changes in the patient's drug treatment not related to current status may be counterproductive, and even lower acceptance rate among physicians if the complexity increases (198). Thirdly, information of drug history essential for the choice of treatment can be lacking. This is an issue also expressed by GPs, that pharmacists in hospitals can be prone to make decisions based on a lack of information (183). Hence, the medication review process implemented in Paper II-III emphasizing the

thorough evaluation of drug therapy regimens and implementation of suggestions was probably not optimal. It was also very time consuming (Paper IV). Shifting towards a focus of identifying DRPs, implementing urgent changes in-hospital, and forward further findings and suggestions to primary care for collaboration and follow-up post discharge, could be an important development of the intervention. Nevertheless, our findings with a median of 4 DRPs per patient, for 25 % of the patients 6 or more DRPs (IQR 2– 6, range 0– 28), highlights that identifying drug related problems in hospital can contribute to drug therapy optimisation and complement primary care. However, conducting fundamental changes to patients' drug therapy regimen might be more suitable when they are in a stable phase, presumably achieved in primary care.

Changes in drug therapy regimens in-hospital and identified issues to be forwarded to primary care demand precise communication with parties involved across the patient pathway. Implementation of the collaborative model contributed to communication about drug therapy across the patient pathway (Paper II-III). The pharmacists contributed to information flow, both in and out of hospital, as well as assuring quality of the information. Decreasing the likelihood of errors and/or uncertainty around drug treatment because of the hospital stay is of immense importance. At the same time, the information step towards primary care GP at discharge was harder to deliver. Furthermore, the emphasis on information delivery at discharge, about changes made and follow-up of suggestions, potentially hampered room for discussions about the drug therapy regimen with the GP. Nevertheless, our focus that collaboration between care levels is essential, remains.

Emphasis on drug therapy optimisation in primary care would increase the number of patients eligible for drug therapy optimisation compared to a during a hospital stay. For example, 75% of Norwegian patients between 70-90 years did not have inpatient stays in hospital in 2021 (27), while 90% of Norwegian patients>65 years are exposed to drug therapy (40). This highlights the need for predictive tools to enable the detection of patients at risk for adverse outcomes, as described previously (100). Even if we have identified that AC/SED drug use increase the risk of PDI in our population (Paper I), the association is not sensitive enough to have potential as a screening tool for the investigated outcome, and the call for screening tools to identify patients at elevated risk for drug related adverse outcomes is highly relevant.

In sum, the findings from this thesis underlines that to ensure continuity in drug therapy and follow-up over time, all levels and steps in the patient pathway should be involved. At the

same time, investigations often implement measures in isolated stages of a patient pathway, rather than integrating care. This is partly the case also in this thesis, where we isolate the hospital stay, although we exchanged information with primary care (Paper II-III). By isolating interventions to one point in patient pathways, the concept of "integrated care" is challenged. Integrated care emphasizes assessing the complete situation for the patients and enabling continuity of care. This is especially important for patient with complex needs (199). Integration of medicines management should follow the patient pathway, including primary care, and active drug therapy optimisation should be a continuous part of health care services. This is supported by a recent consensus principle for clinical practice for frail patients, regular reviews and multidisciplinary communication is emphasised, including different care levels (200). Although in-hospital interventions probably contribute to optimise drug therapy, waiting for hospitalisation for thorough evaluations of drug regimen is not optimal and could lead to loss of function, which is contradictory to the WHO goal to "develop and maintain functional ability"(2). To increase the optimisation process, a potential development could be to establish pharmacist models for drug therapy optimisation across the pathway, with emphasis on primary care, including secondary care as complementary arena. Regardless, our focus on improvement of communication across levels of care as detrimental for drug therapy optimisation should remain.

5.6 Methodological considerations

5.6.1 Strengths

In Paper I, information from the Norwegian health registries, NPR and NorPD provide near complete, reliable, high-quality data (24, 154), eliminating selection bias (201). Merging high quality Norwegian prescription/dispensing data with data from disease-specific registries enabled investigations of outcomes from drug therapy exposure. Further, quality of the variables incorporated in the regression model (Paper 1) were provided by applying reliable methods. The legend approach ensured a high-specificity determination of drug users from pharmaceutical dispensing data (202, 203), while the application of the CCI (156) ensured quality comorbidity assessment to control for in the regression model (Paper I). This thesis applied DBI as a continuous variable, contrary to most trials assessing DBI. One study even eliminated the value of dose adjustment of the drugs by applying DBI as a dichotomous variable (133). Furthermore, the investigation of the linearity of the DBI-exposure variable, indicated that a splined continuous variable represented the data better than a regular unsplined continuous variable.

Observational data are commonly used to assess research questions investigating causality. Causality implies a relationship where an exposure variable directly affects the outcome. However, correlations are not equal to causality (204). In observational trials, confounding variables can interfere with causal relationships and/or cause spurious relationship (201). When building regression models for analysis of large datasets (Paper I), a clinical and theoretical approach is essential to propose causality in the data and to identify potential confounders (204). The cross-sectional design (Paper I) enables control/adjustment for multiple confounders (205), and potential confounders and causality were visualised in a causal diagram, a directed acyclic graph (206). DAGs are increasingly common to use when fitting logistic regression models for a clinical setting as they provide a transparent visualisation of the proposed relationships and enable identification of potential confounders (207). All variables considered relevant for the outcome, based on experience and theoretical knowledge of the field, were incorporated in the DAG. The DAG served as basis for the logistic regression model (Paper I). Moreover, the conclusions in Paper I were based on the combination of effect size and clinical relevance of observed findings.

The RCT design (Paper II-III) create "ideal" conditions to obtain data to determine the efficacy of interventions and is considered the most reliable epidemiological research design (208). The strict control of both population (e.g., randomization) and intervention minimises the risk of confounding factors influencing the results (209). The RCT design does not automatically provide control of the intervention content, contextual factors, and/or the effects on the system in which the intervention takes place (organisational effects). For example, when RCTs investigate complex interventions, they often provide data on efficacy, not addressing transferability to real life practice, effectiveness, and efficiency of the interventions proposed (157, 210). These factors are imperative for the evaluation of results. Deviations from the intended intervention (Consort checklist item 5) (211), performance bias (212), is essential to control in evaluation and interpretation of the results from the trial (212). The inclusion of a fidelity assessment (Paper III) supplies details on deviations from the RCT-protocol (Paper II), providing a transparent, systematic evaluation of "dose delivered" (157) while the process outcomes (Paper III) provide details on the results of intervening.

Furthermore, we evaluated the RCT-intervention by time assessment of the pharmacists providing the service (Paper IV). WOMBAT, with predefined categories, provides little opportunity to affect the content of the tasks, and the careful category design based on the aim of the study ensured a functional observational tool for this RCT-setting (159, 160). Fidelity, process outcomes and pharmacist time distribution enable both a detailed evaluation of the primary outcomes from the intervention in Paper II, including cost analysis, which is planned.

5.6.2 Limitations

In Paper I, NorPD does not provide data on over-the-counter drugs or differentiate between as needed and regular use, and we have no means to control adherence to therapy. However, good correspondence between self-reported adherence to NorPD dispensing data has been shown (213). In addition, our regression model does not include potential confounders, such as socioeconomic status, frailty and living arrangements, due to lack of access to the variables (Paper I). However, previous studies of older persons' health care utilisation found that the direction seen of associations were not changed by demographics and socioeconomic factors, although living alone increased hospital use. Neither was found to affect prescription drugs in use (214). We also lack information from the hospital stay, and we do know that changes in drug therapy is common during hospitalisation (197, 215).

Control and intervention patients in the RCT (Paper II+III) were included from the same wards, and the study pharmacists presented and discussed solutions for intervention patients' DRPs during pre-round meetings. If experiences from intervention patients were used for decision-making for control patients, affecting the main outcome of the trial, it would introduce contamination bias (201). In addition, the start-up period together with switching study-pharmacists during the inclusion phase might have affected the delivery of the intervention over time, potentially introducing chronological bias (216). The prolonged inclusion phase increased the risk of such bias. Furthermore, efficacy in the strictly controlled RCT-study setting does not necessarily transfer to real world practice (217). To understand why, or why not, an intervention works can be equally important as the effect in a controlled environment (218, 219). Complementary aspects to address are for example quality of the delivered intervention, the competence of the pharmacists, and system factors such as setting and sub-culture (211). This would be in line with the call for high quality data on "what works best in health care" (220).

On the other hand, a complex intervention (221) such as the integrated medicines management model (Paper II+III) has the potential to influence factors beyond the efficacy of the intervention. Furthermore, barriers, and facilitators for the delivery of the intervention can explain outcomes from the studies (157, 222, 223). These issues must be actively investigated since they are not met by standard RCTs (220). Supplementary information concerning the delivery of the intervention and potential organizational effects of the intervention was not conducted before, during or after the implementation of the IMMENSE study, which is a limitation. We do not have information on the quality of the delivery, adherence to protocol (i.e., the delivery within each intervention step) and participant responsiveness. When aiming for a "yes/no" answer to clinical outcomes, the complex intervention's full potential, such as organisational changes or benefit for other health care professionals is not investigated (224). Complementary questions remain to be asked and answered when investigating the full value of the intervention. Consequently, an RCT might not be the best way to investigate complex interventions as grounds for implementation of the service. To find "what works best in health care", a pragmatic RCT could be an option (217).

At the same time, the fact that both study wards have implemented clinical pharmacists in the interdisciplinary team at the ward post-inclusion indicate that there must be perceived value regardless of the main outcome of the trial.

5.6.3 Validity of findings

Validity defines to which extent we can be confident in conclusions from the results of scientific studies (225), addressing the presence of systematic error (226). The internal validity mostly concerns the study design; is it appropriately planned to investigate relationships (cause and effect), and exclude other factors as causes of the outcome? The external validity addresses to which extent the results are valid in other settings (227).

One issue with observational study design (Paper I) is the potential of lowered internal validity (227). In Paper I, the internal validity was strengthened by the adjusting for confounders identified in the DAGitty approach to the regression modelling. The observational, cross-sectional design in Paper I indicates high external validity, enhanced by the full population data (227). The results are most likely relevant for similar populations within Norway. Nevertheless, the results will probably not be generalizable across borders, primarily due to expected differences in health care, including available drugs on the marked.

In contrast, the selected population and controlled setting in an RCT limits the external validity (227). The population in Paper III is less likely representative for "older patients" in general due to the selection criteria for participation and the limited inclusion area (two wards). On the other hand, internal validity in RCT's is often considered high due to the controlled setting (227). However, high internal validity require control of the intervention content. Factors affecting the internal validity of the intervention (Paper II) is only partly addressed by the fidelity assessment (Paper III). We know the fidelity of the steps delivered, but not the delivered content of each step. In addition, measuring intervention content include factors such as quality of the delivery, adherence to protocol, differentiation of components and participant responsiveness. Hence, the details essential for the intervention delivery to be reproducible (228) is missing, affecting the evaluation of internal validity.

6 Conclusion

This thesis has generated new knowledge of drug therapy optimisation for older Norwegian patients: a) the drug burden is high in older patients acutely admitted to hospital in Norway, and assessing AC/SED drug burden has the potential to reduce the risk of post-discharge institutionalisation, and b), the pharmacist identify drug related problems and most likely increase the quality of drug therapy in-hospital, they contribute to interdsiciplinary collaboration, and address implementation factors by facilitating communication across the patient pathway. These are initiatives that can contribute to the optimisation of drug therapy for older patients, but it takes time, and can be costly. More studies are needed to identify what measures and/or combination of steps will be most effective in drug therapy optimisation. Furthermore, it is essential to establish models for drug therapy optimisation *across* the patient pathway, including primary care as an essential setting, and determine where in the patient pathway intervention steps are most efficient.

7 Future considerations

Our findings in Paper I suggests that a clinical approach to decrease the risk PDI in older adults could simply be to focus on reducing the number of AC drugs. This should be further explored. Furthermore, knowledge of high-risk drugs, and effects on outcomes is essential to optimise prescribing. In the Norwegian setting, the identification of AC properties revealed issues with availability and access to such information. The development of a consensus-based criteria list of drugs with AC properties could contribute to drug therapy optimisation for the older patients. Equally important is a standardisation of information for prescribers and other involved health care personnel, for example by using the same terminology. Furthermore, making the information easily accessible, is a step towards safer prescribing of these drugs for older patients. This could be solved by incorporating information through the most common informational channels, such as NCCP, or by electronic prescriber systems.

The results from the implemented RCT (Paper II) will be analysed, and the results evaluated in context of the supporting research (Paper III+IV). Furthermore, the intervention should be evaluated in a real-life setting. Future investigation of the pharmacist intervention should address ways to maintain or increase the fidelity of the intervention when less time is available per patient. In addition, one potential improvement of the intervention is to advance the intervention into primary care post-discharge in line with the increased focus on pharmacist interventions continuing post-discharge (229, 230). Adding an intervention step where health care professionals in hospital, such as pharmacists, are dedicated to drug therapy follow-up post-discharge, in collaboration with patient, care teams and prescriber, could improve continuity and safety of drug therapy and decrease fragmentation of care. Pharmacist transitional care can for example include direct patient contact and ongoing contact with primary care teams (177, 231, 232).

Other factors to consider when addressing drug therapy optimisation are: Where in the patient pathway can interventions generate best results? Increased focus on integrated care can be one answer, as suggested in this thesis. An integrated medicines management model involving pharmacists should be a part of integrated care, as well as pharmacists in primary care. An aim should be to develop working models across the patient pathway. Nevertheless, this requires a structural and financial framework, as well as a thorough evaluation of the services.

Higher level ponders

Numerous studies aim to document the value of clinical pharmacy services by investigating different models, including various steps and services, in different health care settings. They often aim to demonstrate impact on hard endpoints such as health care utilisation and mortality. However, a fundamental question to ask is: do clinical pharmacy services have to impact hard endpoints to have a value? I believe a principled discussion regarding clinical pharmacy research is in place in Norway. One shift of evaluations of clinical pharmacy services could be to aim for non-inferiority compared to standard care regarding main outcomes. However, complementary research, assessing the potential benefits of collaboration and pharmacists in the interdisciplinary teams must be conducted, including organisational effects. This should be studied in practice, also allowing for learning from the process by performing complementing research, beyond fidelity and time distribution.

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Paper I

Is anticholinergic and sedative drug burden associated with postdischarge institutionalization in community-dwelling older patients acutely admitted to hospital? A Norwegian registry-based study

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Abstract

Purpose: Investigate the association between anticholinergic (AC) and sedative (SED) drug burden before hospitalization and post-discharge institutionalization (PDI) in community-dwelling older patients acutely admitted to hospital.

Methods: A cross-sectional study using data from the Norwegian Patient Registry and the Norwegian Prescription Database. We studied acutely hospitalized community-dwelling patients ≥70 years during 2013 (N=86,509). Patients acutely admitted to geriatric wards underwent subgroup analyses (n=1,715). We calculated drug burden by the Drug Burden Index (DBI), use of AC/SED drugs, and the number of AC/SED drugs. Piecewise linearity of DBI vs PDI and a knot point (DBI=2.45) was identified. Statistical analyses included an adjusted multivariable logistic regression model.

Results: In the total population, 45.4% were exposed to at least one AC/SED drug, compared to 52.5% in the geriatric subgroup. AC/SED drugs were significantly associated with PDI. The DBI with Odds Ratios (ORs) of 1.11 (95% CI 1.07-1.15) for DBI<2.45 and 1.08 (95% CI 1.04-1.13) for DBI≥2.45. The number of AC/SED drugs with OR of 1.07 (95% CI 1.05-1.09). The AC component of DBI with OR 1.23 and the number of AC drugs with OR 1.13. In the subgroup, ORs were closer to 1 for AC drugs.

Conclusions: The use of AC/SED drugs was highly prevalent in older patients before acute hospital admissions, and significantly associated with PDI. The number, or just using AC/SED drugs, gave similar associations with PDI compared to applying the DBI. Using AC

drugs showed higher sensitivity, indicating that to reduce the risk of PDI, a clinical approach could be to reduce the number of AC drugs.

Keywords: Older patients; Hospitalisation; Institutionalisation; Anticholinergics; Sedatives; Drug Burden Index; National Health Registries.

KEY POINTS

- The use of AC/SED drugs was highly prevalent in older patients before acute hospital admissions
- We found significant relationships between AC/SED drug burden and post-discharge institutionalization, independent of whether we applied DBI scores, the dichotomous variable "using AC/SED drug(s) or not", or the number of AC/SED drugs used, both combined and separately.
- Number of AC drugs had the strongest association with PDI and reducing exposure to AC drugs can potentially reduce the risk of PDI in older hospitalized patients.
- The odds ratios for AC drugs and PDI were closer to one for the subgroup of patients admitted to a geriatric hospital ward, although not statistically significant.
- The Drug Burden Index method is complex. Several steps must be completed before DBI calculation can be executed, and the DBI scores can be challenging to use.

Plain language summary

Anticholinergic (AC) and sedative (SED) drugs are considered high-risk drugs for older patients. This study investigated if the use of anticholinergic (AC) and sedative (SED) drugs before hospitalization increased the risk of institutionalization (PDI) for older patients when they are discharged from hospital. We used data from the Norwegian Patient Registry and the Norwegian Prescription Database to study acutely hospitalized community-dwelling patients ≥70 years during 2013. Patients acutely admitted to geriatric wards (=geriatric group). underwent additional analyses. We measured the patients AC/SED drug burden by i) the Drug Burden Index, ii) whether they used AC/SED drugs (yes or no), and iii) the number of AC/SED drugs in use. We found that 45.4% and 52.5% of the patients used one or more AC/SED drug in the total population and in the geriatric group, respectively. AC/SED drug use increased the risk of PDI in the population for all measurements. Number of AC drugs in use showed the highest risk of PDI in the full population, but not in the geriatric group. Our findings indicate that to reduce the risk of PDI in older patients, one approach could be to reduce the number of AC drugs in use.

1. Introduction

Older people generally prefer to live at home to maintain autonomy (1, 2). However, age-related factors like frailty, falls and cognitive impairment increases the risk of institutionalization such as admission to nursing homes (3-7).

After acute hospitalizations, older people are commonly institutionalized, permanently, or temporarily (8). Risk factors for acute hospital admissions are age and frailty (9), while predictors for the transition to institutions remain uncertain (8). Norway has a "de-institutionalization" policy to manage the aging population (10), an unparalleled extended use of home care services to allow older people to remain home-dwelling longer before institutionalization. This policy is cost-effective and has reduced the proportion of older adults living in nursing homes (11, 12). Therefore, identifying risk factors preventing institutionalization after acute hospitalization is important to target interventions that may enable older people to remain home-dwelling.

Inappropriate drug use in older people is common (13) and known to cause serious harm (14). The use of anticholinergic (AC) and/or sedative (SED) drugs is associated with acute and unpredictable adverse effects to which older patients are particularly susceptible (14). Having this in mind, developing tools that could guide prescribers and health care personnel to take appropriate actions and reduce drug burden is highly relevant. Interestingly, common AC/SED effects such as agitation, cognitive impairment, and dementia-like symptoms (14) coincide with risk factors for institutionalization in older people, thus posing a potential for intervention and improvement.

The Drug Burden Index (DBI) measures the cumulative AC and SED drug burden (15, 16). The DBI is widely used to assess AC/SED-burden in database studies (17) and is associated with adverse health outcomes and functional decline in older people (15, 18-24). In general, associations between drug therapy and post discharge institutionalization (PDI) have rarely been investigated (8), while the association between DBI and PDI has not been examined.

In this study, we investigate the association between AC/SED drug burden and PDI following an acute hospital stay among community-dwelling older people and for a subgroup of patients acutely admitted to geriatric wards, i.e., specialized aged care hospital wards, in Norway.

2. Method

2.1 Study design and data source

For this cross-sectional population-based study, we used data from the Norwegian Patient Registry (NPR) and the Norwegian Prescription Database (NorPD). NPR contains complete data on hospitalized patients (25), while NorPD contains complete information on prescription drugs dispensed from Norwegian pharmacies to community-dwelling persons except nursing-home residents (26). Linking of registries is possible by applying the unique personal identification number assigned all Norwegian citizens. NorPD classify drugs based on the World Health Organization Anatomical Therapeutic Chemical (ATC) classification system (27) and includes: strength/concentration, amount, unit, administration form, and defined daily doses (DDD) dispensed (28). Data from both registries was available from the date of first hospital admission in 2013±1 year.

2.2 Study population

The study population, see Figure 1, comprised community-dwelling persons ≥70 years with at least one admission to a somatic hospital. From NPR, we defined the first hospital stay in 2013 as the index stay (IS), except for patients with stay(s) at geriatric wards where we defined the IS as the first geriatric stay. We excluded patients with elective ISs, with >1 IS on the same date, outpatient stays, and those without a principal discharge diagnosis.

We classified and included patients as community-dwelling if they had at least one dispensed prescription drug identified in NorPD during 120 days before admittance, see Figure 1. We used the discharge status from NPR to identify whether a patient was discharged to an institution (including rehabilitation and nursing homes) or to *other*. The *other* category included patients who died during the hospital stay or were discharged home. Patients in the *other* category were defined as dead during the hospital stay and excluded if they met the following criteria: registered as dead between IS and date of data extract, with no hospital admission (NPR) and no medication dispensing (NorPD) after the IS's day of discharge.

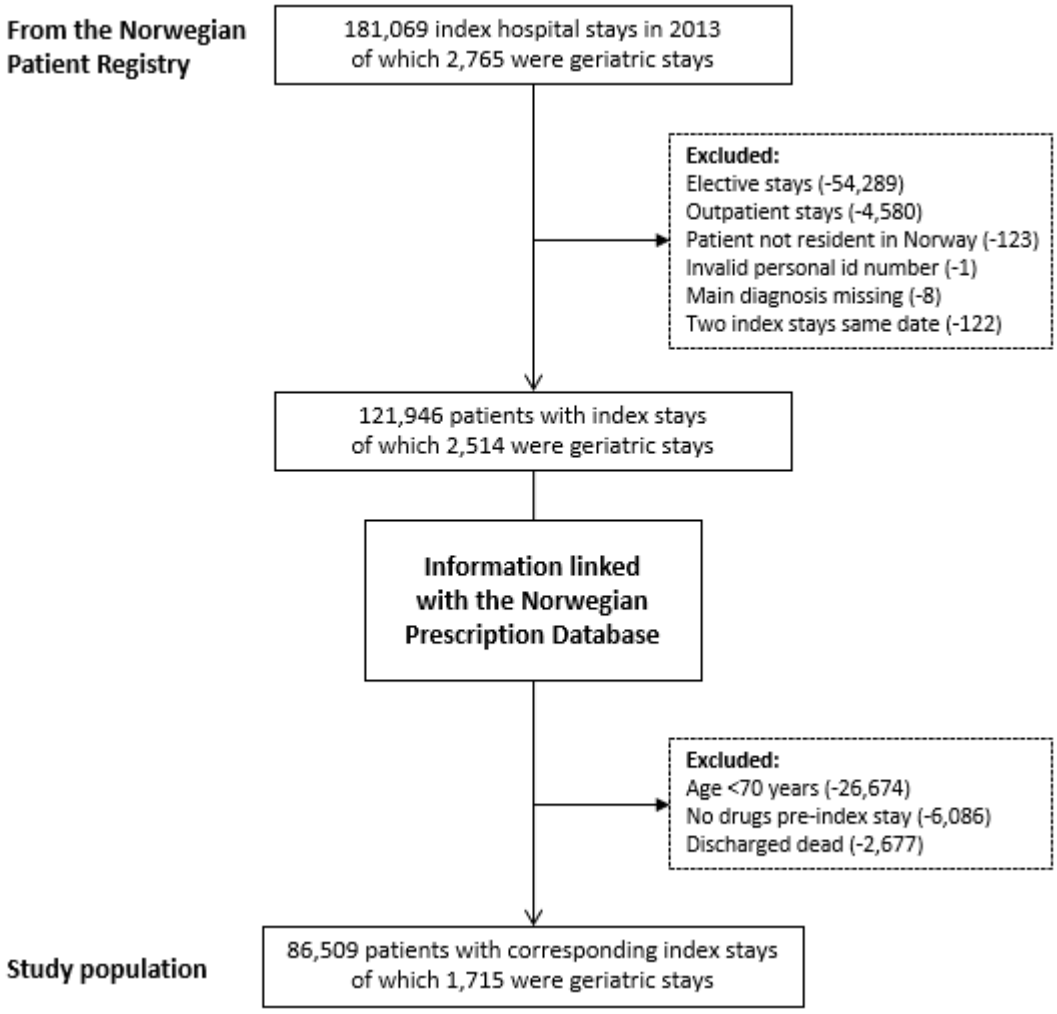

FIGURE 1 Flowchart describing the inclusion process and data merging for the study population.

2.3 AC/SED-drug exposure at hospital admission

We defined drugs (n=135) with anticholinergic and sedative properties, see Supplementary material 1. Drugs with AC properties were defined by searching in The Norwegian Pharmaceutical Product Compendium (NPPC) (29), while drugs with SED properties were defined using the ATC-groups for "primary sedative" and "sedation as a prominent side effect" drugs as described by Linjakumpu *et al*. (30).

We identified exposure to AC/SED drugs at hospital admission by identifying the most recent pharmacy fill for each drug and applying the legend duration approach (31, 32). A drug was defined as 'in use' if the dispensing lasted to the day of admission. Drug exposure assessment is displayed in Figure 2.

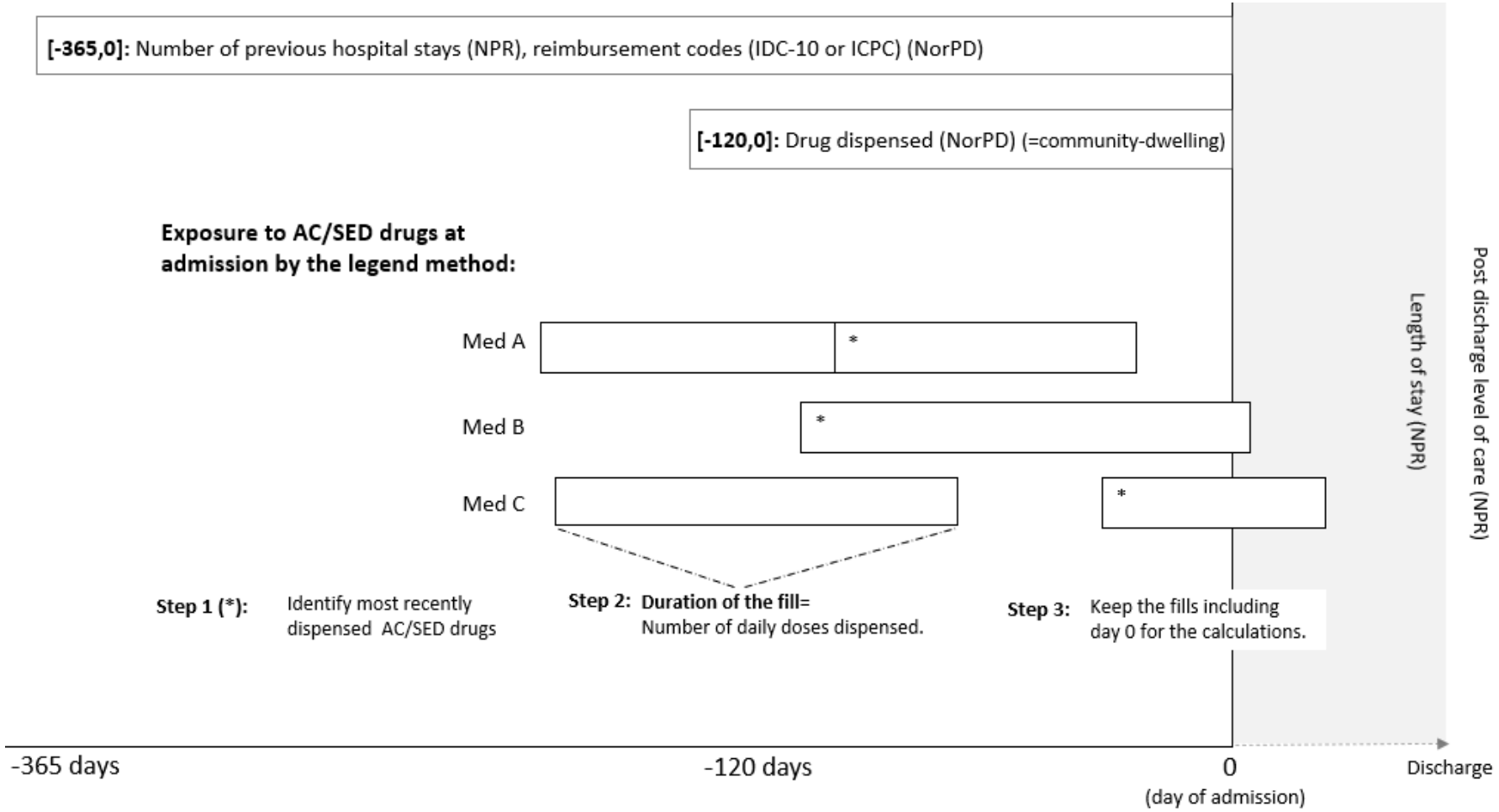

FIGURE 2 Data sources and method used to determine AC/SED drug exposure, length of index stay and postdischarge level of care. Data was collected one year before and after hospital admission (day 0). **Top:** Assessment of previous hospital stays and reimbursement codes one year prior to hospitalisation. Status as community-dwelling was determined by using NorPD data 120 days prior to hospitalisation. **Bottom:** Exposure to AC/SED-drugs at admission using the legend method (31) followed a three-step process: 1. We identified the most recent (re)fills for each drug defined as AC or SED, 2. Duration of the fill was estimated through the number of daily doses dispensed, i.e., daily dose (D)=dispensed unit strength of drug*number of daily administrations, except for drugs with DDD (=defined daily doses(28)) as only information, then duration of the fill= number of DDDs dispensed, and 3. If the most recent fill lasted through day 0, it was defined as **in use** and included in the calculations. Hence Drug A will not be included in the DBI, while drugs B and C will. The dotted arrow between day of admission (0) and discharge indicates length of index hospital stay (shaded area).
AC=Anticholinergic, SED=sedative.

2.4 Drug burden index calculation

The DBI measures cumulative exposure to AC/SED drugs through dose-response based calculations using the DBI expression (15):

$$\boldsymbol{DBI} = \sum \frac{\boldsymbol{D}}{\boldsymbol{D}+\delta}$$

This is a hyperbolic function where each AC/SED drug contributes to the DBI-score with a value between 0 and 1, calculated by daily dose (D) adjusted by the minimum recommended daily dose (δ). For example, a prescribed daily dose of $1* \delta$ will contribute to the DBI-score with a value of 0.5, while increasing the dose to a daily dose of $2* \delta$ increases the DBI to 0.67. Two separate drugs in minimum dose results in a DBI-score of 1. Hence, increasing the dose by one δ contributes to the DBI-score less than adding a DBI-drug in one δ.

Daily doses (D) in use were estimated in step 2 of the legend approach, see Figure 2. We calculated the DBI-score using the minimum recommended maintenance dose collected from the NPPC applying the following criteria: i) the defined adult dose (or for older adults if specified), ii) for drugs with multiple indications, the lowest minimum dose, iii) for combination drugs, minimum dose for the AC/SED component, iv) for drugs with different administration routes, minimum dose for each administration route, v) if two administration routes with same ATC-code were dispensed the same day, doses were converted to equivalents in the DBI-calculations, and vi) for drugs without listing in NPPC, i.e., without Norwegian marketing approval, the minimum dose was set to one DDD.

2.5 Outcome

The outcome variable, postdischarge institutionalisation (PDI), describes whether patients were discharged from the hospital to an institution or not.

2.6 Covariates and factors

The number of hospital stays previous year, main ICD-10 diagnosis for the hospital stay and length of index stay were collected from NPR. Comorbidity was addressed using reimbursement codes, i.e., ICD-10 or ICPC-2 from the NorPD by applying the Deyo adaption of the Charlson Comorbidity Index (CCI) (33). We also constructed a *mental illness-variable* by using reimbursement codes defining mental disorders which the CCI did not cover. From NorPD, we collected information on age and number of drugs dispensed to each patient 120 days before admission.

2.7 Statistical analysis and modelling

Data management, descriptive analysis and DBI calculations were performed in SPSS (version 26), while the regression model was designed and analysed in STATA MP16.0. Descriptive statistics are presented as means with standard deviations (SD) or frequencies with proportions (%). We applied Student's t-test to compare means (continuous data; age, Charlson Comorbidity Index, previous hospital stays, number of drugs used, length of hospital stays and DBI mean score). We considered *P-values<0.05* statistically significant.

The linearity of DBI with the outcome variable was investigated in a weighted scatterplot to identify piecewise linearity, and where the linear pieces met, i.e., corresponding knot points. Subsequently, we used the DBI in the regression model as a splined variable (34). Splining the DBI provide opportunity to include slope changes without categorizing the variable.

The association between AC/SED exposure were investigated by 1. DBI at admission and PDI, 2. use of AC/SED and PDI and 3. the number of AC/SED drugs and PDI. In all situations, we applied a multivariable logistic regression model to estimate the odds ratio (OR) with 95% confidence intervals (CIs). Variables for the regression model was selected by using a directed acyclic graph created in DAGitty v3.0 causal diagram (35, 36), see Supplementary material 2.

2.8 Data access and ethical approval

The regional ethics committee and the Norwegian Data Protection Authority approved the study (REK-reference: 2014/2182, Project number 25995).

3. Results

The study population comprised 86,509 patients of whom 1,715 comprised the subpopulation with geriatric IS. The mean number of drugs dispensed 120 days before admission was 7.1 for the total study population and for the geriatric subgroup. In the total study population, 24.6% were discharged to an institution, compared with 42.5% in the geriatric subgroup. Study population characteristics are presented in Table 1.

Table 1. Characteristics of the total study population and the geriatric subgroup.

Patient characteristics	*Total population* N=86509		*Geriatric subgroup* n=1715	
Age (years), mean (SD)	81.5	(7.0)	85.0	(6.6)
Min, max	70	105	70	101
Female, n (%)	48964	(56.6)	1092	(63.7)
Discharged to institution, n (%)	21281	(24.6)	729	(42.5)
Charlson Comorbidity Index score, mean (SD)	2.0	(1.8)	1.9	(1.8)
Min, max	0	15	0	14
No. of hospital stays previous year, mean (SD)	3.6	(7.8)	3.0	(6.1)
Min, max	0	206	0	162
No. of drugs pre-index stay, mean (SD)	7.1	(4.0)	7.1	(3.8)
Min, max	1	35	1	28
Discharge diagnosis*, n (%)				
Diseases of the circulatory system	21281	(24.6)	405	(23.6)
Diseases of the respiratory system	11246	(13.0)	226	(13.2)
Fractures	8737	(10.1)	22	(1.3)
Symptoms/signs/abnormal findings	8132	(9.4)	206	(12.0)
Diseases digestive system	7613	(8.8)	45	(2.6)
Diseases genitourinary system	4845	(5.6)	146	(8.5)
Mental and behavioral disorders	1298	(1.5)	226	(13.2)
Length of hospital (index) stay, mean (SD)	5.3	(6.0)	8.1	(6.7)
Min, max	1	132	1	72
Anticholinergic and sedative drugs, n (%)				
0	47234	(54.6)	815	(47.5)
1	22492	(26.0)	496	(28.9)
2	10122	(11.7)	232	(13.5)
≥ 3	6661	(7.7)	173	(10.1)
Anticholinergic drugs, mean (SD)	0.19	(0.47)	0.23	(0.52)
Min, max	0	5	0	3
Sedative drugs, mean (SD)	0.58	(0.88)	0.67	(0.91)
Min, max	0	8	0	6
Drug Burden Index, mean (SD)	0.48	(0.68)	0.55	(0.71)
Min, max	0	6.04	0	4.65
Drug Burden Index AC component, mean (SD)	0.11	(0.28)	0.13	(0.30)
Min, max	0	3.11	0	2.17
Drug Burden Index SED[1] component, mean (SD)	0.37	(0.56)	0.42	(0.59)
Min, max	0	5.65	0	4.08

[1] Includes with sedative properties only see Supplementary material 1, **Most frequent registered.*

3.1 Use of AC/SED drugs and DBI

In the total study population, 39,275 patients (45.4%) were exposed to at least one AC/SED drug, compared to 900 patients (52.5%) in the geriatric subgroup. Mean DBI was 0.48 (range 0-6.04, SD=0.68) for the total study population and 0.55 (range 0-4.65, SD=0.71) for the geriatric subgroup. Mean individual contributions of SED and AC drugs to the DBI is given in Table 1.

3.2. Associations AC/SED drugs and PDI

The logistic regression model exploring the association between DBI, use of AC/SED and the number of AC/SED drugs, and PDI is outlined in Table 2. For the full model, including all covariates, please see Supplementary 3. From the scatterplot, we observed a change in the slope and identified the knot point at DBI=2.45. Consequently, for the total study population, the DBI variable was split in two continuous variables comprising 37,371 patients with DBI <2.45 and 1,832 patients with DBI ≥2.45, while for the geriatric subgroup 855 patients had DBI <2.45 and 45 patients had DBI ≥2.45. A DBI increase of one unit significantly increased the odds of PDI in the total study population by OR 1.11 (95% CI 1.07-1.15) and 1.08 (95% CI 1.04-1.13) for DBI< 2.45 and DBI ≥2.45, respectively. A similar effect was not identified in the geriatric subgroup, see Table 2.

Table 2. Multivariable logistic regression presenting the association (Odds ratio, OR) between all drug burden exposure variables, and the outcome postdischarge institutionalisation (PDI) for the total population (n=86,509) and the geriatric subgroup (n=1,694).

	Total population		Geriatric subgroup[§]	
Exposure variables[1]	OR*	(95% CI)	OR**	(95% CI)
Drug Burden Index (DBI)				
Score <2.45 (Spline1)	1.11	(1.07-1.15)	0.99	(0.79-1.23)
Score ≥2.45 (Spline2)	1.08	(1.04-1.13)	1.21	(0.94-1.55)
Only AC component	1.23	(1.15-1.31)	1.08	(0.72-1.61)
Only SED[2] component	1.07	(1.03-1.10)	1.07	(0.87-1.32)
Use of drug with AC/SED properties (yes/no)	1.09	(1.05-1.14)	1.11	(0.86-1.42)
Number of drugs				
with AC/SED properties	1.07	(1.05-1.09)	1.06	(0.93-1.19)
with AC properties	1.13	(1.08-1.17)	1.03	(0.81-1.30)
with SED[2] properties	1.05	(1.02-1.07)	1.06	(0.92-1.22)

[1]The model adjusts for discharge diagnoses according to the ICD10 system, age, number of hospital stays previous year, length of index hospital stay, number of drugs pre-index stay, and Charlson Comorbidty Index score calculated from reimbursement codes of drugs used according to the Norwegian Prescription Database. [2]Includes drugs on the list of drugs with sedative properties only se Supplementary material 1 *Pseudo R2 0.1418, **Pseudo R2 0.1342. [§]OR could not be calculated for 21 patients since all geriatric patients with two categories of discharge diagnoses had same outcome=predicted failure perfectly. See Supplementary material 3.

When the splined variables were replaced with the use of AC/SED drugs (yes/no) per patient, the ORs changed slightly for the total study population to 1.09 (95% CI 1.05–1.14) and for the geriatric subgroup to 1.11 (95% CI 0.86–1.42). Replacing the splined variables with the number of AC/SED-drugs combined had a similar effect, i.e., changing the ORs for the total study population to 1.07 (95% CI 1.05–1.09) and for the geriatric subgroup to 1.06 (95% CI 0.93–1.19). Replacing the splined variables with DBI for the AC component and number of AC drugs in use increased the OR for the study population, with OR 1.23 (95% CI (1.15,

1.31) and OR 1.13 (95% CI 1.08, 1.17) respectively. Replacing with SED component/number of drugs slightly decreased the associations in the study populations. In all situations, the results remained only significant for the total study population.

4 Discussion

This is the first study to describe the prevalence of AC/SED drugs at hospital admission in Norwegian community-dwelling older patients and investigate its association with PDI following an acute hospital stay. We identified high prevalence of AC/SED drugs (45%), and even higher in the geriatric subgroup (52%). We also observed a statistically significant association between AC/SED drug use and PDI, independent of which approach used, where number of AC drugs had the strongest association with PDI. In the geriatric subgroup, this association was not observed.

4.1 Principal findings and implications

Although the prevalence of AC/SED drug use in our study was high, it is comparable to other studies reporting prevalence from 32-62% (23, 37-39). One reason for the considerable variation between studies, may be that no international consensus exists concerning which drugs to be defined as AC/SED drugs. Consequently, comparisons between studies should be done with caution. Nevertheless, our findings confirm a high drug burden amongst these older patients.

We identified significant associations between AC/SED drug use at hospital admission and PDI which indicate that an acute hospital admission is an opportunity to initiate actions to reduce drug burden in older patients, as also suggested by others (40). Surprisingly, the ORs related to AC drugs were closer to one in the geriatric subgroup compared to the total study population, but the subgroup was too small to get significant associations. The reason for this difference is difficult to explain. Our results may be influenced by the shift towards extended use of home care services in Norway to keep older people home-dwelling for a longer time before institutionalisation. A higher proportion (almost 70% increase) of patient from the geriatric subgroup experienced PDI compared to the total study population, see Table 1, which is contrary to previous findings (41). It is likely this subgroup of patients experienced age related functional decline to a point where admission to a geriatric ward function as an entry point for institutionalisation. Nevertheless, our focus on reducing drug burden in older hospitalized patients should remain, as also pointed out by Egberts et.al. (42).

We found significant relationships between AC/SED drugs and PDI, independent whether we applied DBI, the AC/SED components of DBI, the dichotomous variable "using an AC/SED drug or not", or the number of AC/SED drugs used, both combined and separately. The AC component had the highest OR of 1.23, however, the number of AC drugs in use was more sensitive for PDI, with OR of 1.13 per AC drug, since a one unit increase in DBI require the use of at least two DBI-drugs, as explained in chapter 2.4. Focusing on the burden from AC drugs to decrease the risk of PDI is in line with the findings from Egberts et al, who also found a significant association between number of AC drugs and PDI (OR=1.38) (42).

The complexity of the DBI, involving preparations, calculations, and the implications of the scores, challenges the comprehension of the DBI and the application as a clinical tool. In addition, our findings suggest that reducing the *number* of AC/SED drugs have a stronger impact on the risk of PDI in older acutely hospitalised patients compared to applying the DBI and is also easier to apply.

4.4 Strengths and limitations

The main strength of this study is the use of national high-quality registries with complete data on both hospitalizations and drug dispensing. This enables the inclusion of all relevant hospitalizations and drug dispensing in the population and eliminates selection and recall bias normally associated with observational designs. The fact that all Norwegian citizens can be identified with a unique personal identification number enables linking between databases and the completeness of data.

As the DBI variable is an index, we believe that splining DBI and keeping it as a continuous variable in our regression analysis is a more appropriate choice than using DBI as a categorical independent variable (16, 21, 43). This is also in line with the development of the DBI (15). Given the variations in how to estimate individual AC/SED drug exposure (especially for pharmacy database exposure calculations), which impacts the prevalence of these drugs and the magnitude of calculated DBI, it seems unlikely that the same cut off values or intervals should apply to all DBI-data.

AC/SED exposure was defined applying dispensing data from pharmacy records. Prevalence is affected by drugs included and choice of look back period, which affects the sensitivity. To appropriately define drug use, we chose to use the legend approach that provides good estimates of drug exposure at a fixed time point (31). This has not previously been used for daily dose estimates in DBI studies. On the other hand, to determine legend duration by using the daily

dispensed unit strength of drugs multiplied by number of daily administrations, is a more reliable estimate of drug exposure than Defined Daily Doses (DDD) (44). This approach also gives individual DBI-scores mirroring the clinical setting, reflecting known drug-unit strengths. Due to expected variability in non-adherence patterns for the drugs included as AC/SED-drugs, especially for psychotropic drugs (44, 45), we chose not to add grace periods (46). By applying dispensing data from pharmacies, an underestimation of AC/SED exposure may have occurred, as only drugs dispensed from pharmacies are included, and not over the counter drugs and herbal medicines (26). Neither do we have information on hospital-dispensed drugs and consequently no adjustments in exposure to AC/SED drugs during the hospital stay. This may have underestimated drug exposure, as we know that drug use may increase during hospitalisation in older patients (47), that number of potentially inappropriate medications not necessarily are decreased (47), and that hospital stays may increase the exposure to AC/SED drugs (48).

5. Conclusions

The use of AC/SED drugs is highly prevalent in older patients before acute hospital admissions, and significantly associated with postdischarge institutionalisation (PDI) in the study population although not in the subgroup of patients admitted to geriatric wards. Applying the number of AC/SED drugs, or just using or not using AC/SED drugs gave similar associations with PDI compared to applying the drug burden index (DBI). The strongest association was found for number of AC drugs in use. This indicates that a clinical approach to prevent PDI in older patients could simply be to focus on reducing the number of AC drugs. This should be further explored.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementaries Paper I

Supplementary 1, Drugs included as AC/SED-drugs

General information

To avoid duplicates, drugs with both AC and SED properties were classified as AC in line with the original evaluation of DBI (Hilmer SN et al. A drug burden index to define the functional burden of medications in older people. Archives of internal medicine. 2007;167(8):781-7. **doi**:10.1001/archinte.167.8.781). Formulations with a systemic route of administration (injections, oral, transdermal and spray for systemic uptake) were included in the analysis.

Drugs with anticholinergic properties

Pharmacological substance	ATC WHO level 5	Also SED properties
Alimemazine	R06AD01	
Amitriptyline	N06AA09	Yes
Atropine	A03BA01	
Biperiden	N04AA02	Yes
Carbamazepine	N03AF01	Yes
Chlorprothixene	N05AF03	Yes
Clomipramine	N06AA04	Yes
Clozapine	N05AH02	Yes
Cyclizine	R06AE03	
Darifenacin	G04BD10	
Disopyramide	C01BA03	
Dronedarone	C01BD07	
Escitalopram	N06AB10	Yes
Fesoterodine	G04BD11	
Glycopyrronium Bromide	A03AB02	
Hydroxyzine	N05BB01	Yes
Hyoscyamine	A03BA03	
Levomepromazine	N05AA02	Yes
Loratadine	R06AX13	
Meclozine	R06AE05	
Mirtazapine	N06AX11	Yes
Nortriptyline	N06AA10	Yes
Olanzapine	N05AH03	Yes
Oxybutynin	G04BD04	
Oxycodone	N02AA05	Yes
Perphenazine	N05AB03	Yes
Prochlorperazine	N05AB04	Yes
Promethazine	R06AD02	
Quetiapine	N05AH04	Yes
Scopolamine	A04AD01	Yes
Solifenacin	G04BD08	
Trimipramine	N06AA06	Yes

Drugs with sedative properties

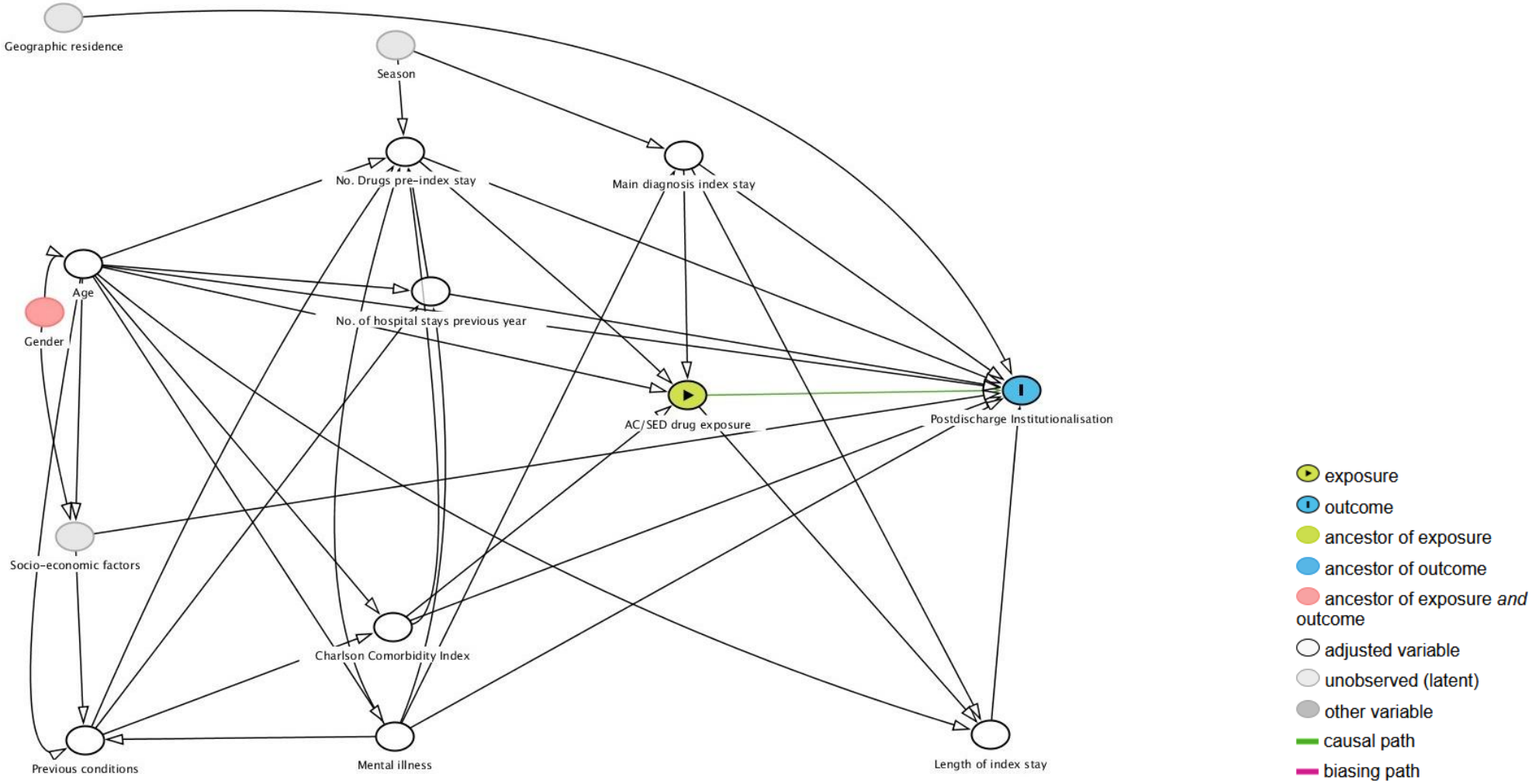
Pharmacological substance	ATC WHO level 5
Almotriptan	N02CC05
Alprazolam	N05BA12
Amisulpride	N05AL05
Aripiprazole	N05AX12
Baclofen	M03BX01
Brexpiprazole	N05AX16
Brivaracetam	N03AX23
Buprenorphin	N02AE01
Buspirone	N05BE01
Cariprazine	N05AX15
Chlorproethazine	N05AA07
Chlorpromazine	N05AA01
Citalopram	N06AB04
Clobazam	N05BA09
Clomethiazole	N05CM02
Clonazepam	N03AE01
Clonidine	N02CX02
Codeine	R05DA04
Codeine and acetaminophen	N02AJ06
Combinations	R05DA20
Dexmedetomidine	N05CM18
Diazepam	N05BA01
Doxepin	N06AA12
Droperidole	N05AD08
Duloxetine	N06AX21
Eletriptan	N02CC06
Eslicarbazepine	N03AF04
Ethylmorphine	R05DA01
Felbamate	N03AX10
Fentanyl	N02AB03
Fluoxetine	N06AB03
Flupentixol	N05AF01
Fluphenazine	N05AB02
Flurazepam	N05CD01
Fluvoxamine	N06AB08
Fosphenytoin	N03AB05
Frovatriptan	N02CC07
Gabapentin	N03AX12
Haloperidol	N05AD01
Hydrocodone	R05DA03
Hydromorphone	N02AA03
Hyperici herba (St. John's Wort)	N06AX25
Ketobemidone	N02AB01
Ketobemidone og spasmolytics	N02AG02
Lacosamide	N03AX18
Lamotrigine	N03AX09
Levetiracetam	N03AX14
Lithium	N05AN01
Lorazepam	N05BA06
Loxapine	N05AH01
Loxapine	N05AH01

Lurasidone	N05AE05
Melatonin	N05CH01
Melperone	N05AD03
Meprobamate	N05BC01
Metoclopramide	A03FA01
Mianserin	N06AX03
Midazolam	N05CD08
Morphine	N02AA01
Naratriptan	N02CC02
Nitrazepam	N05CD02
Noscapine	R05DA07
Oxazepam	N05BA04
Oxcarbazepine	N03AF02
Paliperidone	N05AX13
Paroxetine	N06AB05
Passionflower	N05CM-
Penfluridol	N05AG03
Perampanel	N03AX22
Pethidine	N02AB02
Phenobarbital	N03AA02
Phenytoin	N03AB02
Pimozide	N05AG02
Pregabalin	N03AX16
Propiomazine	N05CM06
Reboxetine	N06AX18
Risperidone	N05AX08
Rizatriptan	N02CC04
Rufinamide	N03AF03
Scopolamine	N05CM05
Sertindole	N05AE03
Sertraline	N06AB06
Sumatriptan	N02CC01
Tapentadol	N02AX06
Theofylline	R03DA04
Thioridazine	N05AC02
Tiapride	N05AL03
Topiramate	N03AX11
Tramadol	N02AX02
Tramadol and acetaminophen	N02AJ13
Triazolam	N05CD05
Trifluprомazine	N05AA05
Valerianae radix	N05CM09
Valproic acid	N03AG01
Venlafaxine	N06AX16
Vigabatrin	N03AG04
Vortioxetine	N06AX26
Ziprasidone	N05AE04
Zolmitriptan	N02CC03
Zolpidem	N05CF02
Zonisamide	N03AX15
Zopiclone	N05CF01
Zuclopenthixol	N05AF05

Drugs with both anticholinergic and sedative properties, classified as AC.

Pharmacological substance	ATC WHO level 5
Amitriptyline	N06AA09
Biperiden	N04AA02
Carbamazepine	N03AF01
Chlorprothixene	N05AF03
Clomipramine	N06AA04
Clozapine	N05AH02
Clozapine	N05AH02
Escitalopram	N06AB10
Hydroxyzine	N05BB01
Levomepromazine	N05AA02
Mirtazapin	N06AX11
Nortriptyline	N06AA10
Oxycodone	N02AA05
Olanzapine	N05AH03
Perphenazine	N05AB03
Prochlorperazine	N05AB04
Quetiapine	N05AH04
Scopolamine	A04AD01
Trimipramine	N06AA06

Supplementary 2 - Directed Acyclic graph from DAGitty (http://www.dagitty.net/)



Supplementary 3-Regression model

Multivariable logistic regression, presenting the association between the splined exposure variable DBI and the outcome Post discharge institutionalisation, with included covariates for the total population (N) and the subgroup comprising the patients with index stay at a geriatric ward (n).

Exposure DBI, outcome postdischarge institutionalisation.	**Total population (N=86509)**		**Geriatric subgroup (n=1694*)**	
	OR	**[95% Conf. Interval]**	**OR**	**[95% Conf. Interval]**
DBI< 2.45 (Spline1)	**1.11**	**(1.07-1.15)**	0.99	(0.79-1.23)
DBI ≥2.45 (Spline2)	**1.08**	**(1.04-1.13)**	1.21	(0.94-1.55)
Age (years)	**1.07**	**(1.07-1.08)**	**1.04**	**(1.02-1.06)**
No. of hospitalisation in the 365 days before admittance.	1.00	(0.99-1.00)	1.01	(0.99-1.03)
No. of drugs dispensed in the 120 days before admittance.	**0.99**	**(0.98-0.99)**	**0.95**	**(0.92-0.99)**
Mental illness	**1.48**	**(1.41-1.55)**	1.09	(0.82-1.45)
Charlson Comorbidity Index.	1.00	(0.99-1.01)	0.97	(0.90-1.04)
Main discharge diagnosis (ICD10)				
A00-B99 Certain infectious and parasitic diseases	**0.75**	**(0.68-0.82)**	0.61	(0.32-1.16)
C00-D48 Neoplasms	**0.77**	**(0.71-0.84)**	0.75	(0.38-1.46)
D50-D89 Diseases of the blood and blood-forming organs	**0.48**	**(0.40-0.56)**	0.35	(0.11-1.15)
E00-E90 Endocrine. nutritional and metabolic diseases	0.90	(0.79-1.02)	1.05	(0.59-1.88)
F00-F99 Mental and behavioral disorders	**1.82**	**(1.61-2.05)**	**1.54**	**(1.08-2.20)**
G00-G99 Diseases of the nervous system	**0.55**	**(0.49-0.62)**	0.65	(0.41-1.05)
H00-H59 Diseases of the eye and adnexa	**0.21**	**(0.14-0.31)**	1*	(empty)
H60-H95 Diseases of the ear and mastoid process	**0.25**	**(0.17-0.36)**	1*	(empty)
I00-I99 Diseases of the circulatory system **(base)**	**1.00**	**Base**	1.00	Base
J00-J99 Diseases of the respiratory system	**0.77**	**(0.72-0.81)**	0.80	(0.56-1.14)
K00-K93 Diseases of the digestive system	**0.45**	**(0.41-0.48)**	**0.31**	**(0.14-0.71)**
L00-L99 Diseases of the skin and subcutaneous tissue	**0.75**	**(0.60-0.93)**	2.22	(0.51-9.56)
M00-M99 Diseases of the musculoskeletal system and connective tissue	**0.84**	**(0.76-0.92)**	1.41	(0.81-2.47)
N00-N99 Diseases of the genitourinary system	**0.80**	**(0.74-0.86)**	0.97	(0.64-1.46)
Q00-Q99 Congenital malformations. deformations and chromosomal abnormalities	0.66	(0.24-1.85)	n.a	n.a
R00-R99 Symptoms. signs and abnormal clinical and laboratory findings	**0.38**	**(0.35-0.41)**	**0.48**	**(0.33-0.71)**
S00-T98 Injury. poisoning and certain other consequences of external causes (-fractures)	**1.20**	**(1.11-1.30)**	2.32	(1.10-4.90)
Z00-Z99 Factors influencing health status and contact with health services	**0.69**	**(0.57-0.82)**	0.53	(0.14-1.99)
Fractures from injury.	**3.61**	**(3.42-3.82)**	2.41	(0.87-6.62)
Length of stay	**1.09**	**(1.08-1.09)**	**1.15**	**(1.12-1.17)**
_cons	0.0006	(0.0005-0.0008)	0.01	(0.00-0.06)

Bold=statistical significance**. 1*** for the main discharge diagnosis ICD10; H00-H59 Diseases of the eye and adnexa, and H60-H95 Diseases of the ear and mastoid process, failure is predicted perfectly, and observations were dropped; 3 and 18 observations not used. Total population: LR chi2(26) = 13681.63, Pseudo R2 = 0.1418. Geriatric subgroup: LR chi2(23) = 310.83, Pseudo R2 = 0.1342

Paper II

BMJ Open

Interdisciplinary collaboration across secondary and primary care to improve medication safety in the elderly (IMMENSE study): study protocol for a randomised controlled trial

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ABSTRACT

Introduction Drug-related problems (DRPs) are common in the elderly, leading to suboptimal therapy, hospitalisations and increased mortality. The integrated medicines management (IMM) model is a multifactorial interdisciplinary methodology aiming to optimise individual medication therapy throughout the hospital stay. IMM has been shown to reduce readmissions and drug-related hospital readmissions. Using the IMM model as a template, we have designed an intervention aiming both to improve medication safety in hospitals, and communication across the secondary and primary care interface. This paper presents the study protocol to explore the effects of the intervention with regard to healthcare use, health-related quality of life (HRQoL) and medication appropriateness in elderly patients.

Methods and analysis A total of 500 patients aged ≥70 years will be included and randomised to control (standard care) or intervention group (1:1). The intervention comprises five steps mainly performed by pharmacists: (1) medication reconciliation at admission, (2) medication review during hospital stay, (3) patient counselling about the use of medicines, (4) a comprehensible and patient-friendly medication list with explanations in discharge summary and (5) postdischarge phone calls to the primary care level. The primary outcome is the difference between intervention and control patients in the rate of emergency medical visits (acute readmissions and visits to emergency department) 12 months after discharge. Secondary outcomes include length of index hospital stay, time to first readmission, mortality, hip fractures, strokes, medication changes, HRQoL and medication appropriateness. Patient inclusion started in September 2016.

Ethics and dissemination The trial was approved by the Norwegian Centre for Research Data and the Norwegian Data Protection Authority. We aim to publish the results in international peer-reviewed open access journals, at national and international conferences, and as part of two PhD theses.

Trial registration number NCT02816086.

Strengths and limitations of this study

- ► No randomised controlled trial investigating the effects of implementing an integrated medicines management-based intervention in the Norwegian healthcare setting has yet been published.
- ► National healthcare registries will enable us to collect high-quality data for several outcomes including the primary outcome.
- ► Collecting outcomes for a 1-year period after discharge allows us to measure sustainable effects of the intervention.
- ► Including control and intervention patients from the same wards may introduce education and contamination bias.
- ► As the intervention is complex this study will not allow for studying whether any of the specific steps are more or less responsible for any observed effects.

INTRODUCTION

Healthcare systems across the world are challenged by an ageing population. Ageing is frequently accompanied by morbidity, which increases the need for pharmacotherapy. The increased complexity of medication regimes combined with frailty, reduced cognitive function and changes in pharmacokinetics and pharmacodynamics increases the risk of adverse drug events and other drug-related problems (DRPs) in this population.[1 2]

A DRP is 'an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes'.[3] DRPs include inappropriate prescribing (drug, dose, dosage frequency and dosage form), drug interactions, adverse drug reactions, wrong administration, need for monitoring as well as non-adherence to medication therapy. DRPs occur frequently in the elderly,[4 5] and are associated with an increased risk of hospitalisation, morbidity

and mortality.[6–8] For instance, adverse drug events alone contribute to 30%–40% of acute hospital admissions in the elderly,[9 10] many of them being preventable.[11–14]

Communication barriers across primary and secondary care, multiple prescribers, fragmentation of care and frequent transitions across care levels make hospitalised elderly in particular risk of drug-induced harm.[15 16] To improve the medicines management process in hospitals, pharmacist-dependent methods like medication reconciliation (MedRec), medication review and patient education have been developed and studied.[17–20] The integrated medicines management (IMM) model is based on interdisciplinary collaboration where clinical pharmacists work together with physicians, nurses and patients aiming to optimise medication therapy by preventing and solving DRPs.[21 22] In the IMM model different services like MedRec, medication review, patient counselling and dissemination of correct medication information at transition points are merged together in a systematic way.[21 23] In Northern Ireland, the implementation of the IMM model in hospitals has led to a reduced length of hospital stay and an increased time to readmission compared to standard care.[23 24] Also in Sweden, implementing IMM in single hospital settings has been associated with a reduction in readmissions and drug-related readmissions, improved communication of medication information at transition points and improved quality of medication therapy.[21 25 26] In Norway, pharmaceutical care services in hospitals have since 2010 been based on the methodology embraced by the IMM model.[27] However, no randomised controlled trial investigating the effects of implementing the IMM model in the Norwegian healthcare system has been published.

Based on the IMM model, we have designed an interdisciplinary collaboration structure aiming to optimise medication therapy in hospitals and to improve communication of medication-related issues between secondary and primary care. The aim of the study is to explore the effects of the intervention on healthcare use, health-related quality of life (HRQoL) and medication appropriateness in elderly patients.

Objectives

The primary objective is to investigate the effects of the intervention on rate of emergency medical visits (acute readmissions and visits to emergency departments (EDs)) 12 months after hospital discharge.

Secondary objectives include to investigate the effects on: self-reported HRQoL, acute readmissions, length of index hospital stay, time to first readmission, 30-day readmissions, general practitioner (GP) visit rate, mortality rate, medication appropriateness, medication-related readmissions, medication changes, hip fracture rate and stroke rate.

METHODS AND ANALYSIS

This protocol is developed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement[28] (see online supplementary file for SPIRIT 2013 checklist).

Study design

This is a non-blinded randomised controlled trial with an intervention group and a control group (1:1 ratio). The intervention group receives the intervention, while the control group receives standard care, see figure 1. Study enrolment started in September 2016.

Settings

The study is carried out at two acute internal medicine wards at the University Hospital of North Norway (UNN); a geriatric internal medicine ward at UNN Tromsø and a general acute internal medicine ward at UNN Harstad. The geriatric ward cares for older patients with complex acute medical needs and has consultants specialised in geriatric medicine. The general medicine ward treats patients admitted for stroke, pulmonary, kidney and endocrine diseases as well as patients with geriatric concerns.

Study population

All acutely admitted patients are screened for eligibility and recruited by study pharmacists. Only eligible patients are invited to participate in the study. When written informed consent is obtained from patient or next of kin, the patient is included. Enrolment is only performed when a pharmacist is present. Readmitted study patients are not reincluded, but receive standard care.

Eligibility criteria

Inclusion criteria: age ≥70 years, acutely admitted and willing to provide written informed consent (patient or next of kin). Exclusion criteria: admitted to the study ward more than 72 hours before evaluation of eligibility, moved to and discharged from other wards during the index stay, inability to understand Norwegian (patient or next of kin), considered terminally ill or with a short life expectancy, planned discharged on the inclusion day, occupying a bed in a study ward but under the care of physicians from a non-study ward or if an intervention from a study pharmacist is considered necessary for ethical reasons (before randomisation or in control group).

Randomisation and blinding

After collecting baseline data, patients are randomised into the two study arms using a web-based service supplied by a third party. The randomisation block sizes are concealed and permuted. We stratify by study site. As pharmacists are only involved in intervention patients, blinding of group allocation is impossible for both the patients, pharmacists and medical team. However, the primary analysis will be performed by an investigator blinded for group allocation.

Standard care (control group)

Patients assigned to standard care receive treatment from a team consisting of physicians, nurses, nurse assistants,

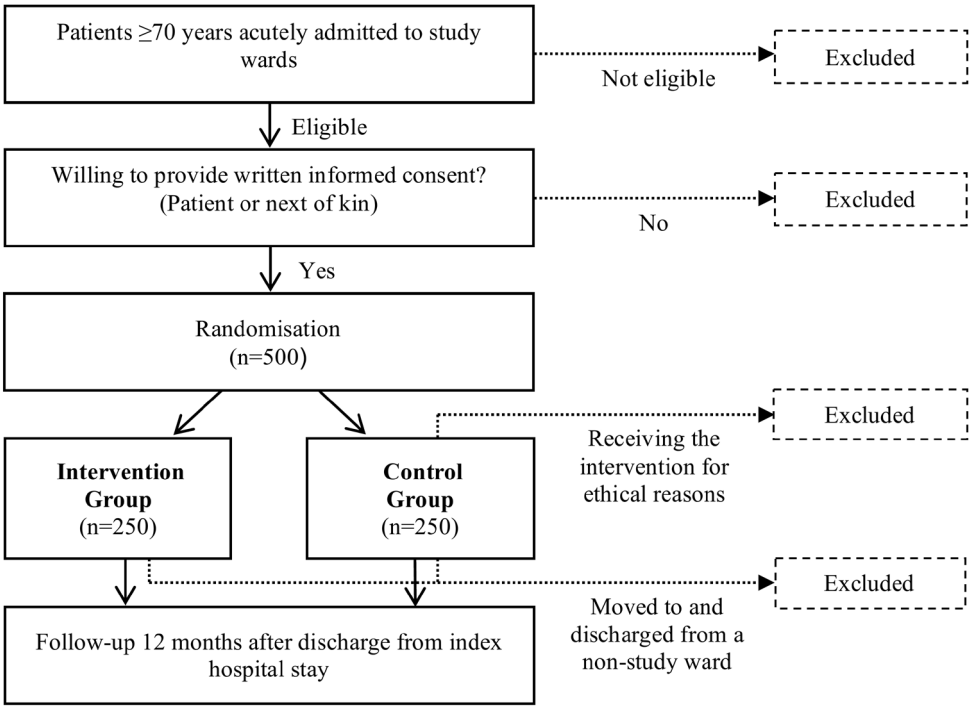

Figure 1 Flow chart of the study and study participants.

and sometimes occupational therapists and physiotherapists. Standard care may include elements as MedRec, medication review and patient counselling performed by physicians or nurses during the hospital stay. However, it is not standardised, structured or involving pharmacists. Study pharmacists are not involved in any clinical work concerning patients randomised to the control group.

Regarding MedRec at admission, this service is currently being implemented in hospitals nationwide as a part of the national patient safety programme. The local hospital procedure at UNN states that MedRec should be performed by a physician at admittance, but local data show that adherence to the procedure is low (data not published). Local procedures for communication of medication information at hospital discharge require that a discharge summary, including an updated medication list in addition to assessments, amendment and recommendations made during the hospital stay, is submitted electronically to the GP at discharge. For patients living in nursing homes or arecared for by the home care services, ward nurses call the home care services or nursing homes to inform about current medication therapy and to investigate the need for prescriptions or medications to be sent home with the patient. The GP is responsible for the follow-up of discharge summary recommendations as well as renewal and revision of prescribed medications.

Patients, for whom special home care is considered necessary, may be referred to a specialised patient care team before or at discharge. This team may include a pharmacist, which may supply pharmaceutical care services.

The intervention

Patients randomised to the intervention group receive the IMM-based intervention including: (1) MedRec at admission, (2) medication review and monitoring during the hospital stay, (3) patient counselling designed to meet the needs of each individual patient, (4) MedRec at discharge together with an updated and structured medication list given to patients and submitted to primary care at discharge and (5) a follow-up phone call to the patient's GP and nurses in home care service/nursing home to inform about and discuss current medication therapy and recommendations, see figure 2. Step 5 is in addition to the original IMM model. The study pharmacist is performing all steps in close collaboration with the hospital physician who has the medical responsibility for the patients.

Step 1: medication reconciliation

MedRec is performed using a standardised MedRec tool developed in Sweden and adapted to Norwegian circumstances/conditions.[21 29] The tool facilitates information collection about the patient's medication use and serves as documentation of information and information sources. It also includes questions about the patients practical handling and knowledge about medications, as well as medication adherence.[21 29] Patients that handle their

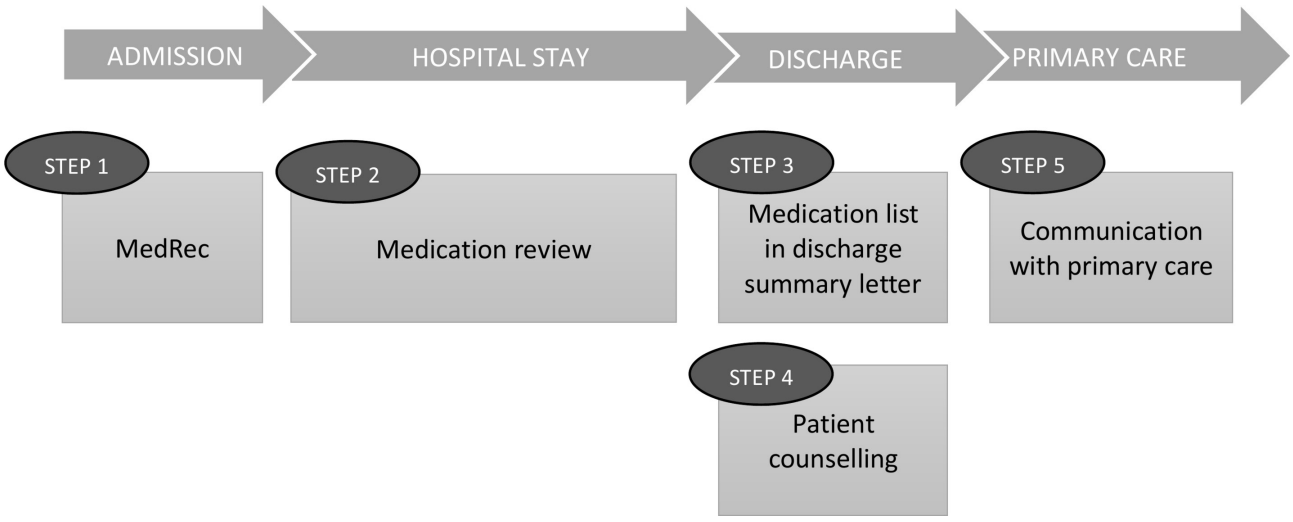

Figure 2 The intervention based on the IMM model (steps 1–4)[21]. Step 5 is added to the original model. IMM, integrated medicines management; MedRec, medication reconciliation.

own medication are interviewed if possible. If not, information about medication use is collected from other relevant sources, that is, medication lists from GPs, national electronic medical records, local pharmacies, home care services, nursing homes or next of kin. These sources are also used to confirm medication information after patient interviews in case of uncertainties. Any adherence or medication information issues identified during MedRec is acted on during patient counselling or at hospital discharge (step 3).

During MedRec, the study pharmacists also perform a standardised symptom assessment to be used in step 2. This is done to identify possible adverse drug reactions, or possible targets for medication therapy improvements from a patient perspective. The assessment is performed to reveal if a patient recently has experienced any of the following 10 symptoms potentially related to medication therapy: dizziness, general fatigue, memory deficiency, sleeping difficulties, dry mouth, nausea, constipation, micturition difficulties, pain or cough. If the patient is incapable of answering the questions, information is obtained from relatives or associated healthcare workers.

Step 2: medication review

Medication review is based on information collected during MedRec, clinical and laboratory data and other relevant information. It is regularly updated during the hospital stay as long as the study pharmacists are present at the ward. A standardised tool, developed in Sweden and adapted to Norwegian circumstances/conditions, is applied to identify DRPs related to the following risk categories[21]: (1) medications requiring therapeutic drug monitoring, (2) potential inappropriate medications for elderly, (3) problems related to drug administration/dosage forms, (4) drug interactions, (5) dose or medications not suitable for the individual patient (eg, renal or liver failure), (6) lack of indication for drug therapy, (7) appropriate length of therapy for temporarily used medications, (8) suboptimal treated or untreated diagnosis or symptoms, (9) medications causing adverse drug reactions or change in laboratory measurements and (10) other needs for monitoring of treatments. Identified DRPs are discussed and solved in the interdisciplinary team and with the patient if possible. DRPs not dealt with or solved during the hospital stay are communicated to the GP as part of the discharge summary together with recommendations and monitoring needs. Identified DRPs are classified according to the validated Norwegian classification system.[30]

Step 3: patient counselling

For patients who will handle their own medication after discharge, a patient counselling session is arranged before discharge. The patients receive an updated medication list, which is discussed and explained. The pharmacists focuses on changes made during the hospital stay and reasons for these changes. Patients are also encouraged to ask questions about their medications. Any medication adherence, handling or information issues identified during the hospital stay is also focused on. If DRPs are identified during this counselling session, they are discussed with the responsible physician. This step does not replace the standard discharge meeting between the physician and the patient.

Step 4: structured and detailed medication list in discharge summaries

The discharge summary normally includes an updated overview of medications to be used after discharge. For intervention patients the study pharmacists draft this list in accordance with hospital procedures and recommendations from the national patient safety programme. They make sure it is reconciled, structured and correct according to amendments done and include information and explanations about medication changes made

during the hospital stay as well as recommendations and follow-up issues. The responsible ward physician uses this draft when preparing the discharge summary.

Step 5: communication with primary care

Within a week after discharge, the pharmacists call the patient's GP to inform about and discuss current medication therapy changes and recommendations stated in the discharge summary. The aim is to ensure that the changes and recommendations are implemented and acted upon.

One the day of discharge, for patients where the home care services or the nursing home administer the patient's medications, the pharmacists call the responsible nurse to inform about medication changes, prescription and monitoring needs and other medication-related recommendations. Changes in multidosage dispensed medications are submitted to the local pharmacy responsible for dispensing the patient's medications in agreement with the home care services.

This step is not carried out for patients with no change in medications during the hospital stay and/or no identified need for follow-up.

Outcomes

Primary outcome

The primary outcome is the rate of 'acute readmissions and ED visits' 12 months after discharge from the index hospital stay in the intervention group compared with the control group. An acute readmission is defined as any subsequent admission following the index admission excluding elective readmissions.

Secondary outcomes (intervention group compared with control group)

1. Change in self-reported HRQoL from discharge to 1, 6 and 12 months after hospital discharge.
2. Length of index hospital stay.
3. Time to first acute readmission after discharge from index hospital stay (up to 12 months follow-up).
4. The proportion of patients readmitted acutely within 30 days (a national quality indicator in Norway).
5. GP visit rate during 12 months' follow-up.
6. Mortality rate during 12 months' follow-up.
7. Change in total score of the Medication Appropriateness Index (MAI) from admission to discharge.
8. Change in potentially inappropriate medications prescribed identified by The Norwegian General Practice—Nursing Home criteria (NORGEP-NH), Screening Tool of Older Persons' Prescriptions (STOPP) V.2 and Screening Tool to Alert doctors to Right treatment (START) V.2 from admission to discharge.
9. Change in potentially inappropriate medications prescribed using START V.2, STOPP V.2 and NORGEP-NH from discharge to 3 and 12 months.
10. Medication changes made during index hospital stay implemented by the GP at 3 and 12 months.
11. Medication-related first readmissions after index hospital stay.
12. Hip fracture rate during 12 months' follow-up.
13. Stroke rate during 12 months' follow-up.

Sample size calculation

Sample size calculation for the primary outcome is based on a Swedish randomised controlled trial applying the same composite endpoint.[12] The Swedish trial investigated the effectiveness of interventions performed by ward-based pharmacists in reducing morbidity and use of hospital care among patients 80 years and older. They randomised 400 patients in a 1:1 relationship and found a 16% reduction in all-cause visits to the hospital in the intervention group. If we estimate a rate of acute hospital admissions and ED visits of 1.7 per year in our control group, we need to enrol 456 patients (228 in each group) to detect a 16% reduction in hospital visits with a significance level of 5% and a power of 80%. To compensate for dropouts, we aim to include 250 patients in each group.

Data collection and tool application

Baseline

Baseline data for all study patients is collected before randomisation to avoid collection bias. This include age, gender, smoking status, marital status, level of education, type and amount of help from home care services, and delivery of multidosage dispensed medications, medical diagnosis/medical history, weight, blood pressure, heart rate, relevant laboratory values (eg, blood creatinine, C reactive protein, haemoglobin and glucose) and medication use at time of hospital admission. The latter is denoted in the handwritten medication chart as standard procedure in our hospitals, while all other information is found in the electronic patient journal.

Hospital stay

For the intervention group only, we collect outcome data from the intervention (eg, discrepancies identified during MedRec, DRPs, physician agreement with regard to identified discrepancies or DRP, counselling issues, etc) during hospitalisation and track communication between pharmacist, patients and healthcare workers in the ward and in primary care. For all study patients, we collect the following data from the discharge summary: discharge diagnose(s), laboratory results, medication list including description of changes during the hospital stay and recommendations to the next care level.

After discharge

Data collection of outcomes after discharge is identical for all study patients.

National registries

Data on readmissions (dates, lengths and reasons), ED visits (dates and reasons), GP visits (dates and reasons), deaths (date and reason), strokes (dates), hip fractures (dates and reasons) and dispensed medications will be collected from six Norwegian Health registries. These

registries are, respectively: The Norwegian Patient Registry (hospitalisations and ED visits), The Norwegian Health Economics Administration Registry (ED and GP visits), the National Cause of Death Registry, the Norwegian Stroke Registry, the Norwegian Hip Fracture Registry and the Norwegian Prescription Database (NorPD) holding information about all pharmacy dispensed medications in Norway. Linking data is possible through the unique personal identification number held by every Norwegian citizen. ED visits leading to a hospital stay will be counted as a hospital stay. We will collect data from all registries for the period 12 months before and 12 months after index hospital stay to enable adjustment for prestudy patterns.

Medication use

In addition to the data on prescriptions collected from NorPD, updated lists of medications in use are collected from GP offices or nursing homes as appropriate at 3 and 12 months after hospital discharge.

Inappropriate prescribing

The medications lists at hospital admission, at discharge and at 3 and 12 months after discharge will retrospectively be subjected to application of the following scoring tools to identify possible inappropriate prescribing by an investigator blinded for group allocation: NORGEP-NH,[31] STOPP and START.[32] The medication lists at admission and at discharge will be scored in accordance with the MAI by an experience pharmacist blinded to group allocation.[33 34]

Health-related quality of life

We use EuroQol 5 dimension (EQ-5D) and EuroQol visual analogue Scale (EQ-VAS) to measure HRQoL.[35] This is performed by a study nurse blinded to group allocation. The measurement is performed at the end of the hospital stay and 1, 6 and 12 months after discharge. The study nurse calls patients and performs the interview by phone. Patients where next of kin provide informed consent are excluded from this measure. We collect information about need for home care services/nursing home at 1, 6 and 12 months to adjust for in the HRQoL analysis.

Medication-related readmissions

An interdisciplinary group of physicians and pharmacists will retrospectively assess whether the patient's first readmission was related to his/her medications and whether it could have been prevented. This will be performed blinded to group allocation.

Data management

All data, except registry data, are entered manually into a Microsoft Access database. A random sample of patients will be drawn for control of data quality. Patient-ID is removed from all paper records and given consecutive study numbers. A list linking patient-IDs to study numbers is stored electronically on the hospital research server, separate from the Microsoft Access database. Only study personnel have access to the research server. Study papers used during work are kept at the hospital in accordance with hospital's patient protection routines.

Statistical analysis

We will use IBM SPSS Statistics V.25 for data analysis. Data will be analysed according to intention-to-treat principle, and the reporting of results will follow the Consolidated Standards of Reporting Trials guidelines.[36] All participants will be included in the analysis, regardless of whether the intervention was completed or not. A per-protocol analysis will also be performed. Descriptive statistics for both study arms and the total study population will be provided.

The primary analysis will be a Poisson regression of the rate of the composite endpoint during 12 months after discharge between the two study groups. Censoring of study participants will be accounted for, and adjustment for study site will be conducted. A two-sided alpha level of 5% will be used. We will perform a secondary analysis of the primary endpoint using the proportion of patients fulfilling the composite endpoint and a survival analysis of the time to reach the composite endpoint. In all analyses, adjustment for baseline variables will be conducted if appropriate.

We will analyse secondary outcomes applying appropriate statistical tests, for example, comparison between study arms by logistic regression analysis for binary responses and using Cox proportional hazards models for survival data. Continuous responses will be analysed using linear regression. A two-sided 5% significance level will be applied, with no adjustments for multiplicity.

The amount of data collected allows for different subgroup analyses and include: to assess whether the effect of the intervention varies by: (1) number of medications at admission or discharge; 0–5, 6–10, >10, (2) age groups 70–79, 80–89 and 90+, (3) patient responsibility for their own medication at discharge, (4) number and type of comorbidities at discharge, (5) number of hospital visits prior to inclusion, (6) length of hospital stay, (7) referred from home, home-care or nursing home or (8) able to self-provide informed consent or not.

ETHICS AND DISSEMINATION

The trial will be conducted in compliance with the protocol, the principles of Good Clinical Practice and the Declaration of Helsinki. Only patients who supply a written informed consent are included in the study. If patients are not able to consent, the next of kin is asked. If a patient is temporarily incapable of giving consent, for instance in the case of delirium, consent is first sought from the next of kin. If and when the patient is again considered able to consent he/she is asked to give the written consent themselves. Patients who refuse participation are excluded from the study.

We will not expose the patient for any new clinical intervention that may put the patient at risk. In fact, some of the elements/procedures included in the intervention

have already been shown to reduce drug-related readmissions, and visits to the ED.[19 20] Nevertheless, our intervention brings a new healthcare profession, the pharmacist, into the interdisciplinary team for whom the patient will have to relate to. We anticipate that patients feeling uncomfortable with this will refuse study participation.

We aim to publish study results in international peer-reviewed open access journals, at national and international conferences, and as part of two PhD theses.

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Competing interests None declared.

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Ethics approval The study has approval from the Norwegian Centre for Research Data and the Norwegian Data Protection Authority to collect, store and link research data.

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Paper III

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ORIGINAL ARTICLE

Intervention fidelity and process outcomes of the IMMENSE study, a pharmacist-led interdisciplinary intervention to improve medication safety in older hospitalized patients

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Abstract

What is known and Objective: The majority of hospitalized older patients experience medication-related problems (MRPs), and there is a call for interventions to solve MRPs and improve clinical outcomes like medical visits. The IMMENSE study is a randomized controlled trial investigating the impact of a pharmacist-led interdisciplinary intervention on emergency medical visits. Its multistep intervention is based on the integrated medicines management methodology and includes a follow-up step with primary care. This study aims to describe how the intervention in the IMMENSE study was delivered and its process outcomes.

Methods: The study includes the 221 intervention patients in the per-protocol group of the IMMENSE study. Both intervention delivery, reasons for not performing interventions and process outcomes were registered daily by the study pharmacists in a Microsoft Access® database. Process outcomes were medication discrepancies, MRPs and how the team solved these.

Results and discussion: A total of 121 (54.8%) patients received all intervention steps if appropriate. All patients received medication reconciliation (MedRec) and medication Review (MedRev) (step 1 and 2), while between 10% and 20% of patients were missed for medication list in discharge summary (step 3), patient counselling (step 4), or communication with general practitioner and nurse (step 5). A total of 437 discrepancies were identified in 159 (71.9%) patients during MedRec, and 1042 MRPs were identified in 209 (94.6%) patients during MedRev. Of these, 292 (66.8%) and 700 (67.2%), respectively, were communicated to and solved by the interdisciplinary team during the hospital stay.

What is new and Conclusion: The fidelity of the single steps of the intervention was high even though only about half of the patients received all intervention steps. The impact of the intervention may be influenced by not implementing all steps in all patients, but the many discrepancies and MRPs identified and solved for the patients could explain a potential effect of the IMMENSE study.

KEYWORDS
aged, hospitalization, integrated medicines management, pharmacists, randomized controlled trial

1 | WHAT IS KNOWN AND OBJECTIVE

Providing optimal medication therapy to patients becomes more challenging with increasing age and morbidity. The majority of hospitalized older patients experience medication-related problems (MRPs), defined as events or circumstances involving medication therapy that actually or potentially interferes with desired health outcomes.[1,2] MRPs can cause serious harm followed by increased morbidity and healthcare costs, and older patients are particularly vulnerable.[3-5] Interventions to identify, prevent and solve MRPs are consequently warranted. Since medication reviews (MedRevs) alone have failed to show improved clinical outcomes,[6,7] interventions should preferably be multifaceted and multi-disciplinary.[7-9] This is the case for the integrated medicines management (IMM) model, a systematic approach that integrates the services medication reconciliation (MedRec), MedRev, patient counselling and correct dissemination of medication information at transition points, holding the clinical pharmacist as a key team member.[10,11] It is recognized that these might be common practices already in some countries. In 2012, the Norwegian hospital pharmacies decided to build their developing clinical services on the IMM model.[12] In Norway, as in many European countries, clinical pharmacy is still a novel role for hospital pharmacists[13]. Pharmacists performing MedRec, MedRev and patient educations as members of interdisciplinary ward teams is not a part of standard care in most hospitals.

The IMMENSE (Interdisciplinary collaboration across secondary and primary care to improve medication safety in the elderly) study is a two-armed randomized controlled trial (RCT) aiming to increase medication safety in older adults over 70 years (ClinicalTrials.gov Identifier: NCT02816086).[14] The intervention comprises an interdisciplinary team collaboration, applying the IMM methodology,[10,15] in addition to post-discharge communication with primary care, see Figure 1. Its primary endpoint is the rate of emergency medical visits (acute readmissions and visits to emergency departments) in intervention vs. control patients 12 months post-discharge.

The multistep intervention in the IMMENSE study aims to improve the complex process of medicines optimization and target different organizational levels. It requires trained pharmacists working in close collaboration with other health professionals and patients, and there will likely be many factors influencing the outcomes of the trial. Information about these factors is necessary to evaluate, interpret and understand the trial results and subsequently implement the intervention in routine practice or design improved interventions.[16] Information about whether the intervention was delivered according to protocol, often defined as fidelity, is important.[17] Process outcomes describe the MRPs identified and how these were solved due to the implementation of the intervention. Together, fidelity and process outcomes can be seen as potential mediators of the relationship between the intervention and its outcomes.[16,18]

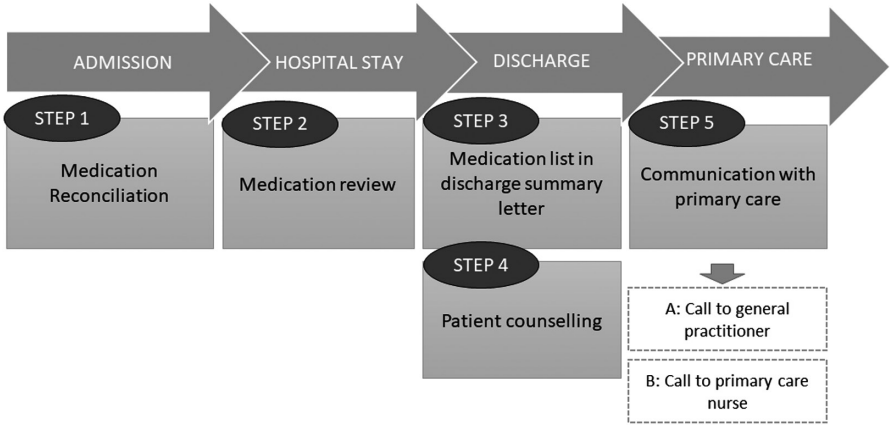

FIGURE 1 Intervention delivered in the IMMENSE (Interdisciplinary collaboration across secondary and primary care to improve medication safety in the elderly) study. Figure adapted from figure 2 in reference [12]

In this study, we aim to describe the IMMENSE study's intervention fidelity and process outcomes (see Table 1 for specific research questions).

2 | METHODS

2.1 | Study design

This study analyses data collected in The IMMENSE study, a two-armed RCT including patients from September 2016 to December 2019, finalizing follow-up in December 2020. The main results are expected in 2022.

2.2 | Setting and intervention

The IMMENSE study was conducted at two medical wards at the University hospital of North Norway.[14] Study ward A was a specialized geriatric acute care ward, with a pharmacist present every weekday from 8 am to 3.30 pm. Study ward B was a general internal medicine ward in a smaller hospital with a pharmacist present every other weekday from 8 am to 3.30 pm. Patients were randomized 1:1 to an intervention or control group. A full description of the intervention can be found in the published protocol.[14] Briefly, the intervention comprised five steps: (1) medication reconciliation (MedRec) at admission, (2) medication review (MedRev) during the hospital stay, (3) a comprehensible and patient-friendly medication list with explanations in discharge summary (draft made by the pharmacist), (4) patient counselling at discharge with updated medication list and (5) post-discharge phone calls to primary care (see Figure 1). Detailed standard operational procedures guided all steps. Control group patients received standard care, that is care *without* a pharmacist in the team.

2.3 | Participants

The IMMENSE study included patients aged 70+ years, as described in the study protocol.[14] Of the 516 included patients, 259 were randomized to the intervention group. The present study includes the 221 intervention patients in the per-protocol group, 181 from study ward A and 40 from study ward B.

2.4 | Data collection

The study pharmacists documented patient information and interventions delivered per patient in a Microsoft Access® study database, in addition to process outcomes (medication discrepancies and MRPs) and results from team discussions. Reasons for not delivering the intervention steps were also recorded. In addition, the pharmacists documented all patient counselling and communication with primary care in the patients' medical records.

2.5 | Intervention fidelity

We used the study database to identify which intervention steps had been delivered to each patient or whether there were protocol deviations when adapting the intervention in real life. For example, the protocol states that the patient's general practitioner should be contacted within 1 week of discharge, but this was not always possible. The full intervention coverage was calculated as the number of patients where the study pharmacist had self-declared delivering intervention steps, also including steps not delivered when not relevant to patients according to the study protocol. For this study, step five was dichotomized as following: a) call to general practitioners and b) call to primary care nurses.

2.6 | Process outcome assessment

A medication discrepancy was defined as an inconsistency between the medication list in the hospital and the medication list obtained by the study pharmacist after a structured MedRec process. Medication discrepancies were categorized applying categories developed and used in the Norwegian IMM procedure, with some local adaptions (Table 2). MRPs identified during MedRev, and considered by pharmacists to be relevant for team discussion, were categorized by applying the validated classification system for MRPs developed by Ruths et al.[19] Recommendations to solve MRPs were classified into 15 categories developed by the research team (Table 2). Outcomes from discussions within the interdisciplinary team were categorized as following: i) recommendation implemented, ii) MRP to be communicated to general practitioners, iii) recommendation not implemented by physician or rejected by patient, iv) implementation status unknown or missing.

2.7 | Data analysis and statistics

We used IBM® SPSS Statistics version 26 and Microsoft® Excel 2019 for data management and analysis. Results are described with numbers, means and standard deviations (SDs). The median, interquartile range (IQR) and minimum and maximum values have been applied for non-normally distributed data.

2.8 | Ethical approval

The IMMENSE study has approval from the Norwegian Centre for Research Data and the Norwegian Data Protection Authority to collect, store and link research data. Informed consent was

TABLE 1 Research questions for this study, table inspired by Kempen et al[24]

	Research questions
Intervention fidelity	What percentage of intervention group patients received the different intervention steps as defined in the study protocol?
	What were the reasons for protocol deviation?
	Is there a difference in fidelity between the two study wards?
Process outcomes	In what percentage of patients did the study pharmacist identify medication discrepancies?
	In what percentage of patients did the study pharmacist identify MRPs?
	What number and types of discrepancies were identified during MedRec?
	What number and types of MRPs were identified during MedRev?
	What proportion of discrepancies were discussed in the interdisciplinary team?
	What types of recommendations were made to solve MRPs?
	What was the outcome of the medication-related discussions in the interdisciplinary team?

obtained from patients or from next of kin when patients were not competent to consent.

3 | RESULTS

3.1 | Study population

Of the 221 patients, 63.3% were females, the mean age was 83.4 (SD 6.3), and the median length of hospital stay was five days (IQR: 3–8.5, range 0–48). Before MedRec, the median number of medications used regularly and as needed were 6 (IQR:4-9, range 0-23) and 2 (IQR:0-3, range 0-11). At discharge, only 49 patients (22.2%) self-administered medications.

3.2 | Intervention fidelity

A total of 121 (54.8%) patients received the full intervention, which was higher in study ward A (58.6%) compared to study ward B (37.5%). Most patients (34.8%) not receiving the full intervention missed only one step (see Figure 2)

Step 1–2. All patients (n = 221) received MedRec and MedRev.

Step 3. A medication list according to the study protocol was present in the discharge summary for 177 patients (80.1%), indicating that physicians used the pharmacist drafts as intended. In 36 patients, the medication list had elements in line with the pharmacist draft but did not fully adhere. The medication list for eight patients was not in line with the study protocol.

Step 4. A patient counselling session (including next of kin for some patients) was performed in 112 patients (50.7%). For 86 patients, patient counselling was not performed because they were not in charge of their medications at discharge. Consequently, 10.5% of the study population did not receive medication counselling when they should have. Only 62 (55.3%) patients received a written medication list as part of the counselling session.

Step 5a. The pharmacists communicated medication changes, the reason for the change, and follow-up issues, including unsolved MRPs, in a phone call to the general practitioner for 153 patients (69.2%). In 28 patients, there were no changes in medications or follow-up issues justifying a call to the general practitoner. Consequently, this step was not delivered for 18.1% of patients. The study protocol states that general practitioners should be contacted within 1 week from discharge, which was achieved for 108 patients (48.9%). The median time from discharge to contact was four days (IQR 2–9, range −1, 34). The primary reason for the delayed contact was difficulties in reaching the physicians.

Step 5b. The pharmacists or the hospital nurses communicated medication changes and monitoring needs to the primary care nurses for 112 and 38 patients (68%), respectively. For 49 patients, no primary care nurse was involved in medication handling, and no follow-up call was necessary. Consequently, 10% of patients missed this step.

3.3 | Process outcomes

3.3.1 | Medication discrepancies during MedRec

The pharmacists identified 437 medication discrepancies (median 1, IQR 0–3, range 0–10) in 159 patients (71.9%), see Table 2. Of the discrepancies, 92.9% were presented to and discussed with the physician, and changes were made in the medication charts for 292 discrepancies (66.8%). The discrepancies involved 164 different medications, most frequently paracetamol and zopiclone involved in 34 and 21 discrepancies, respectively.

TABLE 2 Prosses outcomes identified in the study patients ($N = 221$)

Outcome description	Number identified	Number of patients involved, *n* (%)
DISCREPANCIES DURING MEDICATION RECONCILIATION	437	159 (71.9)
Medication omission	191	101 (45.7)
Regular use	88	
Pro re nata or temporary use	102	
Medication no longer in use	89	52 (23.5)
Frequency/dosing incorrect	82	56 (25.3)
Strength incorrect	41	33 (14.9)
Timing incorrect	22	21 (9.5)
Administration form incorrect	9	9 (4.1)
Medication mix-up (wrong medication name)	3	3 (1.4)
MRPs DURING MEDICATION REVIEW	1042	209 (94.6)
1. Medication Choice	537	181 (81.9)
a) Need for additional medication	158	
b) Unnecessary medication	197	
c) Inappropriate medication choice	182	
2. Dosage	210	124 (56.1)
a) Too high	119	
b) Low dose	53	
c) Sub-optimal dosing scheme	9	
d) Sub-optimal formulation	29	
3. Adverse drug reaction	63	51 (23.1)
4. Interaction	83	60 (27.1)
5. Medication use	29	25 (11.3)
a) Administered by health personnel	5	
b) Administered by the patient	24	
6. Other	120	78 (35.3)
a) Need for/lack of monitoring of effect and toxicity	61	
b) Lack of or unclear documentation of the medication chart /prescription	28	
c) Other	31	

3.3.2 | Medication-related problems during MedRev

A total of 1042 MRPs (median 4, IQR 2–6, range 0–28) were identified in 209 patients (94.6%), see Table 2. The most prevalent MRPs were related to medication choice, identified in 181 patients (81.9%), and dosage, identified in 124 (56.1%) patients. A total of 700 MRPs (67.2%) were solved in the interdisciplinary team in hospital as recommended by the pharmacist, while 239 MRPs (22.9%) were communicated to primary care because the general practitioner was in a better position to initiate and follow-up on changes. For the MRPs discussed with the general practitioner in step 5, 46 were solved, 11 were not solved, and for 182, actions taken by the general practitioner are unknown. Figure 3 shows the distribution of agreement with the different solutions to MRPs proposed by the pharmacist. The medications most frequently involved in MRPs included zopiclone (37 MRPs), paracetamol (35 MRPs), pantoprazole (35 MRPs), polyethylene glycol (30 MRPs) and iron preparations (30 MRPs).

4 | DISCUSSION

4.1 | Intervention fidelity

This study shows an overall fidelity of the IMMENSE intervention of 54.8%, where only one step was missing for most patients not receiving the entire intervention. It is not known which part of the intervention (if any) is the most effective, consequently the implication of missing one or more steps on the trial outcome is unknown. For the single steps, all were delivered to over 80% of patients. An

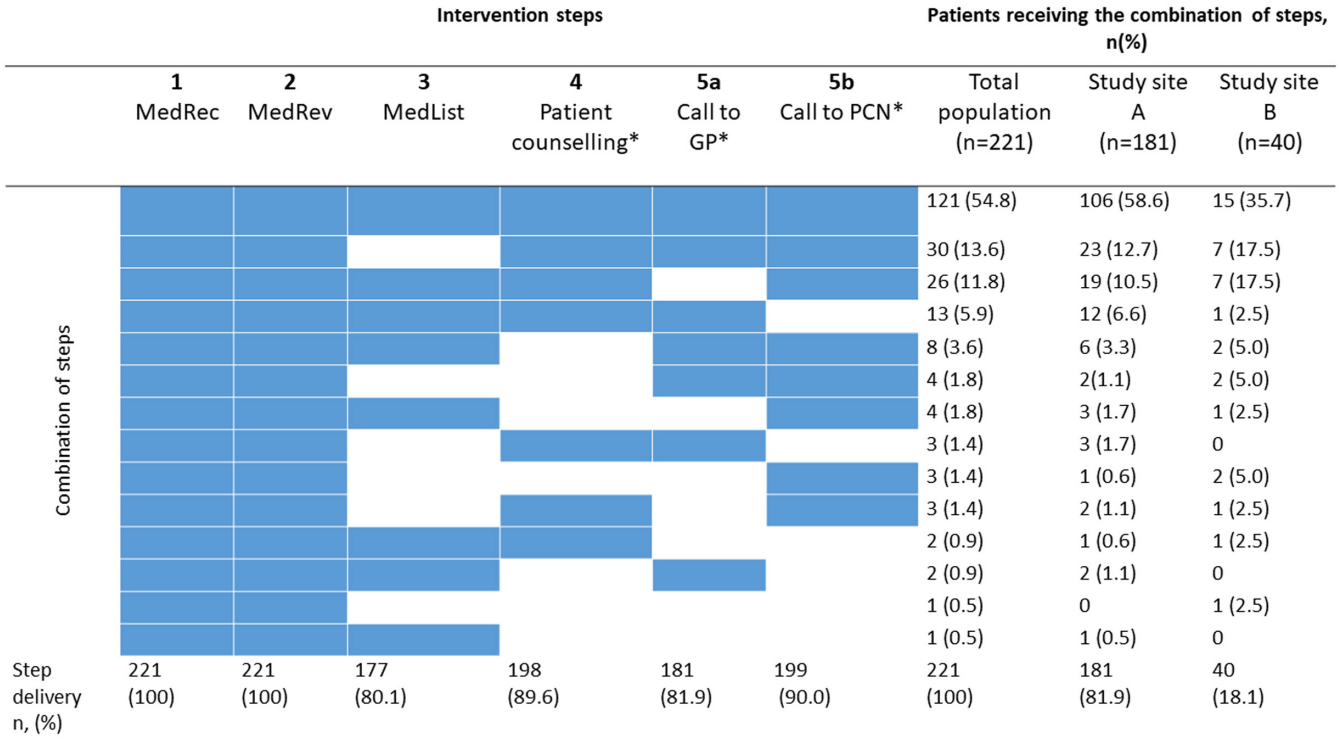

FIGURE 2 Intervention step delivery in the total population and at the two study wards. GP; General practitioner, MedRec; medication reconciliation, MedRev; Medication Review, MedLIst; Medication list at discharge, PCN; primary care nurse *Step delivery includes patients who were delivered the intervention and patients where an intervention was not indicated according to the protocol (ie patients with no primary care nurse)

overall fidelity of 54.8% is in line with other studies showing fidelity of 53–67% of similar complex interventions,[20,21] while many studies do not report overall fidelity.[9,10,22,23]

The study pharmacists performed MedRec and MedRev (step1&2) more frequently than the other steps, which has also been reported by others.[21,24] This may be because the pharmacist can perform both MedRec and MedRev independently of the team if electronic medical records and patients are available. The other steps are associated with more implementation barriers due to dependency of other team members and collaboration partners. For example, handing out written medication lists during patient counselling in step 4 was challenging as lists were often not finalized by the physicians when the pharmacist found time to speak with patients. However, we identified a high proportion (80.1%) of discharge summaries with medication lists according to the study protocol, showing a high fidelity of step 3. Timing of the delivery of the medication list may not be essential to the study results in this study population, as long as appropriate lists were transferred to primary care.

Patient counselling in step 4 was feasible in few patients due to cognitive disabilities and patients not handling medications themselves post-discharge. This may make communication with primary care (step 5) more important, contrary to findings in other patient populations showing patient counselling to be essential in similar interventions.[9] During analysis, we split step five into two sub-steps to clearly show how the intervention was carried out, which also reduces overall fidelity. The challenge of getting in contact with the general practitioner further reduced the fidelity of this step. Still, the pharmacists reached the general practitioner in 153 of the 193 patients with medication follow-up issues, 108 patients within the protocol-defined week. This is high compared with a Danish study by Ravn Nilsen et al.,[9] where the general practitioner was contacted/reached in 55.0% of patients. The authors did not report on time to reach, although their goal was within three working days.

Regarding differences between the study wards, we identified a lower fidelity in study ward B, which was expected as they did not have a full-time pharmacist at the ward. In addition, there was a higher turnover of patients in this ward (data not shown), reducing the opportunity for the pharmacists to follow-up patients.

4.2 | Factors influencing intervention delivery

We believe that slow patient recruitment in the study gave the pharmacists more time to work with individual patients compared to routine practice, which may have increased fidelity. An observational time and motion study on how the IMMENSE pharmacists spent their time identified that pharmacists used on average 3.5 hours performing clinical tasks per intervention patient, 14% of this time communicating with healthcare workers and patients.[25] It is important to note that this does not necessarily reflect the time needed to complete the clinical tasks, but when no new patients are available, more thoroughly performed MedRevs are possible.

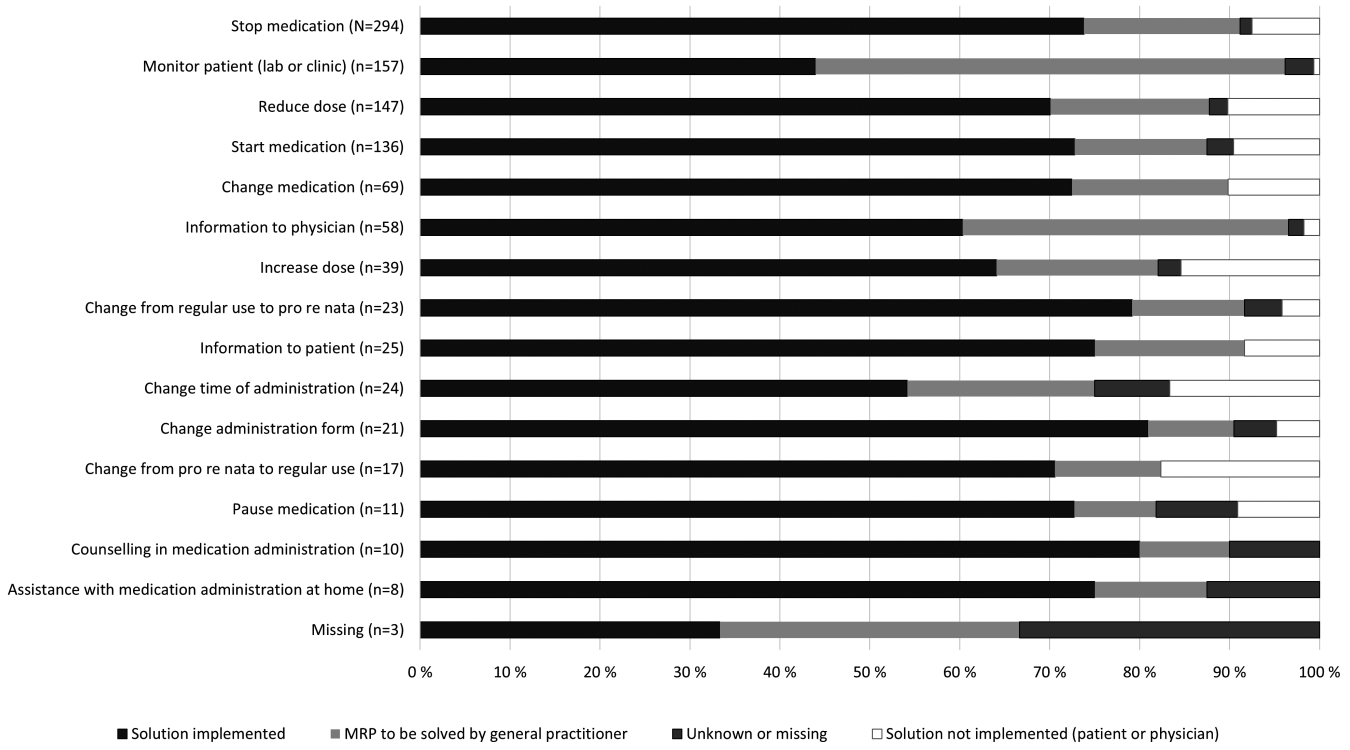

FIGURE 3 Implementation of suggested solutions to medication-related problems (MRPs) after discussion in the interdisciplinary team during the IMMENSE study ($N = 1042$)

Kempen et al. studied facilitators and barriers of ward-based pharmacist intervention in Sweden. They identified unclear roles and responsibilities of the pharmacists, the need to build personal relationships, being present at the ward, and the need for more clinical competence in pharmacists as some of the barriers to performing the intervention.[26] Similar barriers are likely to be present in our study. Having a pharmacist as an integrated team member was new both to the healthcare teams, pharmacists, patients and primary care. After study completion, both study wards have engaged clinical pharmacists in 50% positions working according to the IMM method, indicating that the other team members appreciated the pharmacist input.

4.3 | Process outcomes

The study pharmacists clearly contributed to optimizing medication use, identifying a median of one medication discrepancy and four MRPs per patient in the intervention arm. The number and frequency of discrepancies are in line with other Norwegian studies applying the IMM methodology identifying discrepancies in 70–84% of medical inpatients.[27-29] The number and frequency of MRPs are also in line with previous Norwegian and Scandinavian studies, where MRPs have been identified in 80–100% of hospitalized internal medicines patients,[2,21,23,30] in the range of 2–9 MRPs per patient.[2,22,24,30-32] The number and type of MRPs per patient vary across studies with similar interventions,[21,22,32,33] likely because of the lack of consensus concerning the classification of MRPs.[34] One outlier is the number of MRPs identified in a recently published study by Lea et al.[21] They tested IMM working procedures in an intervention similar to IMMENSE and identified 3826 MRPs in 193 intervention patients giving a mean of 19.7 MRPs per patient.[21] However, only 43% of the identified MRPs were discussed in the multidisciplinary team. Still, the difference from our findings is surprising given the similarity of the interventions and the patient populations. It may be caused by other factors like differences in pharmacist competence, adherence to the IMM procedures, and reporting and classification of MRPs.

The interdisciplinary team appreciated the pharmacist recommendations, as almost 70% were agreed upon. The high agreement rate is in line with other hospital pharmacist intervention studies in Scandinavia, showing agreement rates of 57–75%.[9,20-23,31] A reason for the high agreement in the IMMENSE study may be that the pharmacists discussed MRPs and solutions face-to-face in the interdisciplinary team, in addition to documenting in patients' records. This has been shown to increase agreement rates over written recommendations alone.[35,36]

It is to be expected that 23% of the MRPs identified by the pharmacists were communicated to the general practitioner rather than solved during hospitalization, as the general practitioners are in a better position to monitor patients when the patients are stable in their normal environment. For example, withdrawing sedative medication needs to be done over time in collaboration with the patients.[37] In addition, while optimizing medication use, it is preferable to make medication changes one by one, leaving time to monitor and evaluate the change.[38]

4.4 | Strength and limitations

By collecting and interpreting fidelity and process outcome data before the primary objectives of the IMMENSE study are analysed, we intend to give an unbiased presentation of some factors which may impact the results. The main strength of this study is the prospective day-to-day data collection in the study database as we capture the pharmacist interventions in real time and not through retrospective review, written notes and journal documents. In addition, we used a validated MRP classification system developed for a Norwegian setting and familiar to the study pharmacists.[19]

A significant limitation is that we have only measured what the study pharmacists have entered in the study database, not the quality of the intervention delivered, consequently capturing only the intervention dose delivered.[18,39] To achieve a complete fidelity description, a pre-planned process evaluation should have been performed applying a mix methods approach to measure the quality of intervention delivery, identify barriers to effective implementation, and adoptions to the context at the different study wards.[16]

Another limitation is the clinical relevance of both medication discrepancies and MRPs, as they are clearly not equally relevant. For example, paracetamol was one of the medications most often involved in MRPs and discrepancies. Although improving paracetamol use hopefully will benefit the patient, the use of paracetamol in regular doses is not frequently linked to hospitalizations.[4,40] Evaluating clinical relevance would have strengthened the interpretations of this study.

5 | WHAT IS NEW AND CONCLUSION

In the IMMENSE study, 54.8% of the patients received the full intervention, where only one step was missing in most patients not receiving the entire intervention. MedRec and MedRev were the only steps delivered to all patients. Fidelity was lower at one study ward, showing the need for the pharmacist to be continuously present in order to implement similar interventions. The impact of the intervention may be influenced by not implementing all steps in all patients, but the many discrepancies and MRPs identified and solved for patients could explain a potential effect of the IMMENSE study.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Paper IV

PLOS ONE

RESEARCH ARTICLE

Time distribution for pharmacists conducting a randomized controlled trial—An observational time and motion study

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Abstract

Introduction

An expected future increase in older adults will demand changes in health care delivery, making development, implementation and evaluation of new health care models essential. The rationale for political decision-making concerning the implementation and application of interventions in health care should include cost estimations, specifically those involving clinical interventions. To provide such data knowledge of time spent on the intervention is imperative. Time and motion methodology is suitable to quantify health care personnel's time distribution.

Aim

To investigate the time distribution for pharmacists conducting a randomized controlled trial (RCT) implementing a clinical intervention.

Materials and methods

The setting was an RCT with a 5-step pharmacist-intervention in collaboration with the interdisciplinary team in a geriatric ward. Two pharmacists were involved in the trial during the observation period. Pharmacist activities, classified as RCT-tasks (intervention or administrative), non-RCT tasks and social/breaks, were recorded applying the Work Observation Method By Activity Timing methodology, enabling recording of predefined work tasks as well as interruptions and multitasking. One observer collected data over eight weeks.

Results

In total, 109.1 hours were observed resulting in 110.2 hours total task time, including multitasking. RCT tasks comprised 85.4% of the total observed time, and nearly 60% of the RCT time was spent on intervention tasks. Medication reviews was the most time consuming task, accounting for 32% of the observed time. The clinical pharmacists spent 14% of the

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intervention time communicating verbally, mainly with patients and healthcare professionals.

Conclusion

During the RCT, the clinical pharmacists spent about half their time performing the actual intervention. Consequently, costs for providing such a clinical pharmacist service should reflect actual time spent; otherwise, we may risk overestimating theoretical costs.

Introduction

The predicted future increase in older adults will demand changes to the way health care is delivered. An expansion and/or reallocation of health care spending and human resources across different care settings seems inevitable [1,2]. Consequently, evaluating practice models for health care services, including different health care team collaborations and compositions, has become increasingly relevant.

The randomized controlled trial (RCT) design is suited to evaluate complex health interventions and organizational changes by reducing biases, enabling comparisons of new work models with standard care, and presenting data on defined outcomes [3–6]. In addition, the RCT has substantial potential to provide information on costs related to carrying out interventions [7,8]. To guide the economic evaluation of health interventions The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) was released in 2013 [9]. Ten journals published the standard simultaneously, indicating consensus regarding the need for such guidelines. Nevertheless, a later literature review aiming to support general RCT-planning found only partial reporting of costs in the studies assessed [10]. Similar findings have been reported in Norway [7].

Cost reporting is highly relevant for studies of clinical pharmacy services. Evaluations of the economic implications of such services have shown consistent shortcomings [11–17]. Although most studies present beneficial cost-effectiveness, the variability of study design, outcomes and methods for cost-estimations are substantial, making it difficult to achieve general conclusions. Few studies report full economic evaluations, and if they do the quality is often deemed poor, for example input costs are rarely included in the evaluations [13,16]. Even recent studies of clinical pharmacy services do not adhere to the CHEERS criteria [14].

Health care personnel expenses in clinical trials are often referred to as direct costs (related to an intervention, or the disease) as opposed to the indirect costs (related to loss of productivity, patient perspective) [18,19]. To provide more powerful evidence supporting clinical pharmacy services, a more detailed overview of intervention costs of clinical pharmacy services has been called for [14,16]. Reliable cost estimates of health care interventions depend upon the differentiation between costs of performing the intervention and costs associated with running the study [18]. However, to our knowledge, there are no studies determining how clinical pharmacists spend their time conducting an RCT. This should be of interest for health policy decision-makers responsible for prioritizing and allocating resources to provide efficient and equitable health care, since poorly designed or non-existent cost-estimates may give an inaccurate basis for decision-makers regarding whether to implement interventions or not.

The aim of this study was to investigate the time distribution for pharmacists delivering the clinical pharmacist intervention while also operating day-to-day administrative responsibilities in an RCT.

Materials and methods

Design and setting

We conducted a time and motion study of clinical pharmacists delivering a clinical pharmacy service while performing day-to-day administrative responsibilities in the IMMENSE study [20]. The IMMENSE-study is a two-armed RCT in an acute geriatric ward at the University Hospital of North Norway. The control arm comprised standard care provided by an interdisciplinary team consisting of physicians, nurses, physio-, speech-, and occupational therapists. In the intervention arm, the clinical pharmacists were included in the interdisciplinary team carrying out the following clinical tasks: medication reconciliation at admission, medication review during the hospital stay, patient counselling during hospital stay and at discharge, medication reconciliation at discharge including documentation of a structured medication list, and finally a telephone call to the patients' primary care physician within two weeks after discharge to discuss medication changes and treatment plan, see Fig 1.

During data collection two clinical pharmacists shared a 100% position, delivering the intervention, recruiting and randomizing patients, as well as collecting and documenting study relevant information. They were at the ward weekdays between 8.00 a.m. and 3.30 p.m. (37.5 hours/week).

The observation tool

The time and motion methodology is well suited to collect information about how health care personnel allocate time on different tasks and activities. Such data are widely used to describe and improve production efficiencies in health care systems and commonly used to evaluate costs of provided care [21–23].

For the time and motion observations we applied the validated Work Observation Method of Activity Timing (WOMBAT) methodology [24,25]. WOMBAT comprises continuous observation of workflow, performed by an external observer. Pharmacist activities were recorded by using a tablet (Samsung Galaxy Tab S2) with the validated WOMBAT software downloaded. The software allows for continuous recording of time in multiple dimensions [24,25]. In this study, we recorded the following four dimensions: *what* (task performed), *who* (with whom the observed pharmacist interacts), *how* (by phone, face-to-face, electronic journal and transit) and *where* (the location of the task). The *what*- dimension was mandatory and always recorded, while the other three dimensions were optional [24–26]. When a task with any multiselection of dimension sub-categories was recorded, the software automatically time stamped the interval of each task together with any additional selection. Interruptions (i.e. response to an external stimuli which causes the observed pharmacist to change task) and multitasking (i.e. when two or more tasks are performed simultaneously) are also recorded with time stamps [25].

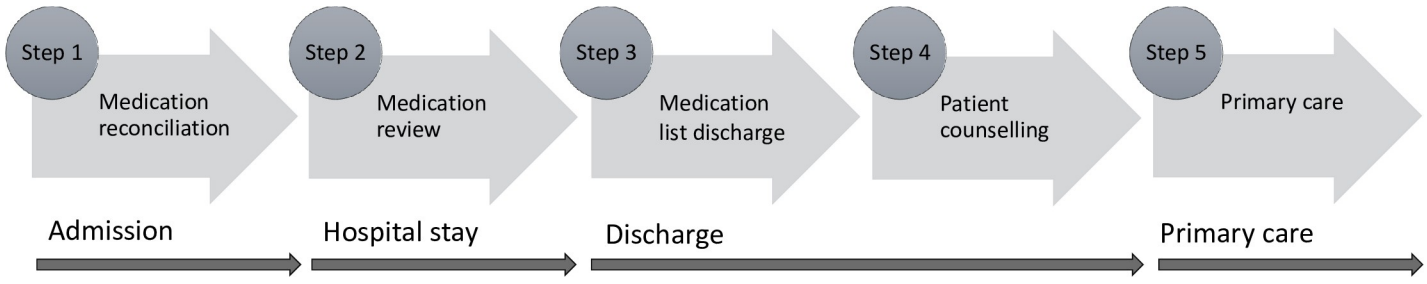

Fig 1. The RCT intervention.

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Table 1. Final version of the WOMBAT observation categories with mutually exclusive definitions.

Dimension	Category	Work task	Definition
What	RCT	Medication reconciliation (i)	Perform medication reconciliation: information gathering, interviews regarding the patients' medication use, communicate findings. *Excludes*: copy charts, plot in study database, write in electronic journal.
		Medication review (i)	Reviewing inclusion patients' medication use: symptom score, documentation, assessing patient journals, databases and guidelines. *Excludes*: plot in the study-database.
		Counselling (i)	Counsel intervention-patients: advice about medicine/health-related issues. *Excludes*: conversation about medication list at discharge.
		Discharge Medication list (i)	Preparing medication lists at discharge: Clarifying medication use, work with lists in electronic journal, guide physicians using the lists. *Excludes*: when lists have status "finished" in electronic journal and is printed.
		Discharge intervention (i)	Review of medication lists at discharge: communication with primary care/patient regarding medication lists, -use and prescriptions. *Excludes*: communication about medication use at admittance.
		Information RCT (a)	Information of RCT to collaborating professions, overlapping RCT-information between study-pharmacists. *Excludes*: explain the study during inclusion.
		Map patient flow (a)	Identifying patient flow: verification of eligibility and ability to consent. *Excludes*: monitor included patients.
		Inclusion RCT (a)	Enrolling patients: preparing forms, providing RCT information to patient/next of kin, getting consent, randomization and documentation. *Excludes*: classification of patient status.
		Registration/ organization (a)	Organizing RCT and registration in study specific systems: printing data, copy charts, filing, and registration in study database. *Excludes*: work with inclusion forms, log data in patient journals.
	Social /breaks	Social/ breaks	Social interaction and breaks: lunch, get drinks, restroom breaks, conversations, private phone calls.
	Non-RCT	Clinical, non-study related	Work regarding patients not included in the RCT.
		Other	Other tasks not already defined, such as turning the computer on/off, retrieving work documents, hospital pharmacy meeting activities.
How			Medium of action: phone (= verbal communication), face-to-face (= verbal communication), electronic journal and transit.
Who			With whom the pharmacist interacts: physician, patient, nurse, next of kin, home care services, pharmacist and other.
Where			Location of performed activities.

(i) = intervention task, (a) = administrative task.

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The categories within each dimension were based on knowledge about the RCT and ward activities. Pharmacist activities (*what*) were differentiated and classified as either 1) RCT-tasks, 2) non-RCT-tasks or 3) social activities/breaks. The latter comprised activities such as not work-related conversations, toilet and lunch breaks, and were not differentiated further. The RCT category, however, was divided into two subgroups: intervention and administration. The intervention tasks evolved from the clinical intervention described in Fig 1, while the administrative tasks were related to conducting the RCT, e.g. including patients, collecting and plotting study data.

The external observer (EL), having extensive WOMBAT experience, and a clinical pharmacist previously involved in the RCT (KH), conducted preliminary observations and piloted the WOMBAT software tool. See Table 1 for the final version of the WOMBAT observation categories, including mutually exclusive definitions describing inclusion and exclusion criteria for each task category and dimension.

Data collection

The external observer, instructed not to interact with either pharmacists, patients or ward staff, observed the clinical pharmacists during an eight-week period and recorded all the tasks they performed during each observation session. Throughout this period 36 patients were asked to participate in the RCT. Of these 30 patients accepted, where 16 were randomized to

the intervention group. A total of 106 patients were admitted during the observation period, of whom 66 were eligible for inclusion. The observation schedule was planned to ensure proportional observation during the pharmacists' working hours. We divided daily working hours into four intervals and restricted each data collection period to a maximum of 1 hour 55 minutes. To avoid observation fatigue we only allowed two data collection periods daily, and never consecutively. The pharmacists were informed about the scheduled observations. After the final observation session, the external observer and the observed pharmacists participated in a debrief (led by KH) to collect information about their experiences of both observing and being observed.

Statistical analysis

Data from the WOMBAT software was downloaded as a comma-separated value (CSV) file and analyzed with the Statistical Analysis Software (SAS) system for Windows, version 9.4. Time spent on each task category was expressed as a proportion of total observation time. Total task time was expressed as time spent on multiple tasks. Interruption rates were generated for relevant categories along with the proportion of time spent multitasking. Furthermore, we generated proportions of time in sub-categories from the defined time-categories and from verbal interaction. We calculated corresponding 95% confidence intervals (CIs,) using a simple bootstrap approach where the 2.5^{th} and 97.5^{th} percentiles of 1000 resampled measures were used as the lower and upper confidence limits.

Ethics approval

As no sensitive information was collected in the study no ethical approval was necessary in accordance with national guidelines in Norway (The Regional committee for medical and health research ethics, Norway, reference number 2017/685). However, both pharmacists consented to be observed, confirmed in writing. We also informed the health care personnel at the ward of the study.

Results

The pharmacists were observed for a total observation time (TOT) of 109.1 hours, giving 110.2 hours total task time due to observed multitasking. The time distribution and proportions of TOT are presented in Table 2.

The clinical pharmacists spent 85.4%, 9.7% and 5.8% of the total observation time on RCT-tasks, non-RCT-tasks and social activities/breaks, respectively. Undertaking RCT-tasks the pharmacists spent 59% of the time (55.3 hours) carrying out the clinical intervention and spent 41% of this time on administrative tasks. While carrying out the intervention most time was spent on medication review (63%) followed by provision of a discharge medication list (19%). Within the administrative tasks most time was allocated to study registration/organization. Of non-RCT tasks, 9.4 hours (89%) was spent on "Other".

The pharmacists were interrupted 1.5 (95% CI 1.1–1.8) times per hour when occupied with the intervention, slightly higher than the observed average interruption rate of 1.3 per hour (95% CI 1.1, 1.5). During the observations, about 1% of the total time was recorded as multitasking, with 250 instances in total. The multitasking presented mostly within the social/breaks category (191 instances, 13% of the social/breaks time). The pharmacists communicated verbally 18.8% of the total time observed. Table 3 displays the communication time distribution.

Social/breaks together with non-RCT tasks consisted of more than 50% verbal communication. However, most of the verbal communication (59.7%) took place during RCT-activities,

Table 2. Distribution of time for all tasks.

Category	Observed time (h)	Percentage of TOT	Sub-category	Work task	Task time (h)	Proportion of TOT (95% CI)	Proportion of intervention specific task time (95% CI)
RCT	93.3	85.5	**Intervention** (55.3 h)	Medication review	34.9	32.0 (28.4–36.8)	63.2 (55.3–71.4)
				Discharge medication list	10.5	9.6 (7.7–11.9)	19.0 (15.1–23.2)
				Medication reconciliation	7.4	6.7 (5.2–8.7)	13.3 (10.0–17.0)
				Discharge intervention	2.2	2.0 (1.2–3.0)	3.9 (2.3–5.8)
				Counselling	0.3	0.3 (0.1–0.7)	0.6 (0.1–1.2)
			Administration (38.0h)	Registration/ organization	25.9	23.7 (20.8–27.4)	n/a
				Map patient flow	5.6	5.1 (4.2–6.4)	n/a
				Inclusion RCT	4.9	4.5 (3.6–5.6)	n/a
				Information RCT	1.6	1.5 (0.8–2.6)	n/a
Non-RCT	10.6	9.7		Other	9.4	8.6 (5.8–12.9)	n/a
				Clinical, non-study related	1.2	1.1 (0.6–1.6)	n/a
Social/ breaks	6.3	5.8		Social/breaks	6.3	5.8 (4.7–7.3)	n/a

Tasks are presented as proportions of total observational time (TOT) and intervention tasks are also specified as proportions of RCT-intervention task time.
h = hours, CI = confidence interval.

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of this 61% was recorded when executing the intervention, which accounted for 14% of the intervention specific time, mainly with physicians (36.8%) and patients (29.8%), see Fig 2.

Discussion

The current study is the first to explore time distribution for pharmacists delivering a clinical pharmacist intervention while also operating day-to-day administrative responsibilities in an RCT. The pharmacists spent a considerable proportion of the observed time performing RCT-administrative tasks, which was expected since RCTs are known to be time-consuming and require extensive administration [27]. Time spent on study administration should be of little importance for key stakeholders assessing whether or not to implement new health care services; thus, the RCT-administrative proportion of the pharmacist time should be omitted from future economic assessment of the intervention. However, these findings may provide valuable information to health care researchers planning similar studies.

The majority of the intervention time (63%) was spent on medication reviews. WOMBAT-studies of real-life clinical pharmacy practice in a children's ward and public hospitals report

Table 3. Distribution of the verbal communication time.

Category	Time (h)	% of total communication time (CI 95%)	RCT subcategories	Time (h)	% of RCT specific communication time (CI 95%)
RCT	12.2	59.7 (50.6, 70.5)	Intervention	7,5	61.0 (49.0, 74.1)
			Administration	4.8	39.0 (28.7, 50.6)
Non-RCT	4.8	23.6 (8.1, 45.4)	n/a		
Social /breaks	3.4	16.8 (11.5, 23.1)	n/a		

h = hours, CI = confidence interval, RCT = randomized controlled trial.

https://doi.org/10.1371/journal.pone.0250898.t003

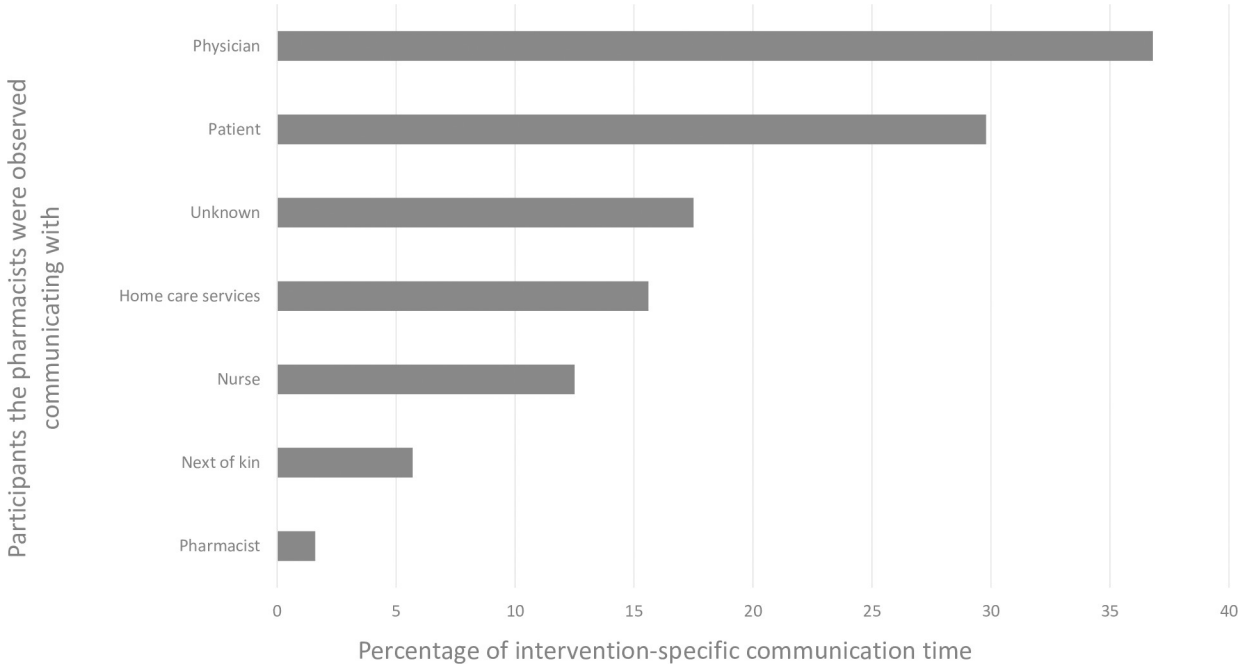

Fig 2. Pharmacist communication during the intervention-specific time (n = 7.1 hours).

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that about 30% of the observed time is spent on performing medication review [26,28]. Although direct comparison is difficult due to the differences in settings, category design and definitions, the proportion appears relatively high and may reflect that the pharmacists valued conducting medication reviews above administrative tasks. Other explanations include that few patients were available for inclusion, no time limits or deadlines for tasks completion had been set [20], and medication reviews were usually presented to physicians the day after inclusion. Also, medication reviews in frail elderly patients with complex medication regimens requires a thorough clinical assessment making them time-consuming. In addition, the pharmacists might have been more thorough in the RCT, knowing that the end results of the intervention would influence the outcomes of the trial.

In contrast, the proportions of time spent on medication reconciliation and the provision of drug information to patients at discharge were low. Both these tasks have rather explicit endpoints and were conducted typically in a semi-structured form with checklists in the RCT.

The total time spent working clinically *per patient* was substantial in the observed study. During the observations, on average 3.5 hours was spent performing clinical tasks per intervention patient. Studies on optimal length for pharmacists performing clinical services in hospitals are scant, but two Swedish trial studies estimate that pharmacists conduct their clinical tasks spending around 30–65 minutes per patient [29,30]. Both these estimates differ notably from our findings to a point where the feasibility of the intervention can be questioned, unless health economic studies of the intervention demonstrate differently.

When working with intervention tasks the pharmacists communicated verbally 14% of the time, mainly with physicians and/or patients. A cross-country WOMBAT study measuring the impact of electronic medication management systems on the work of hospital pharmacists in Australia and England reported above 30% of the observed time spent on tasks implying communication pre and post implementation[28]. Lehnbom et al. reported 25% communication, including medication discussion, in a pediatric hospital setting [26]. Since our study recruited

intervention and control patients from the same ward, and clinical pharmacists were not allowed to engage in matters regarding control patients (to minimize bias), the time spent communicating seems comparable [20]. Even though such behavior might be beneficial when running an RCT, it deviates from the role expected of clinicians working in interprofessional teams [31], adding to the differences between the observed setting and clinical practice.

Implications of findings

By quantifying the time clinical pharmacists spend on different tasks we enable estimations of pharmacist costs in future economic evaluation of the provided health care service. Our presentation of the clinical pharmacists' time distribution is highly relevant in the evaluation of the observed study's outcomes, facilitating a detailed overview of pharmacist costs in accordance with the CHEERS criteria [9]. But more interestingly, the study demonstrates inevitable transferability issues, pointing to limitations by using results from a fixed study design to provide sound cost estimates of a real-life clinical service. On the other hand, our results support the importance of conducting accurate planning. They could also be used to recalibrate workflow efficiency of similar services by suggesting appropriate time allocation to individual tasks.

Strengths and limitations

The main strength of this study is the observational category framework in combination with the WOMBAT software, enabling exact time registration of activities, similar to what has been described when measuring time distribution of physicians, nurses and pharmacists in various hospital settings [22,26,32–36]. The comprehensive development of categories based on the RCT structure reflects the workflow in a multidimensional clinical study, and made measurement an easy task. Moreover, all observations took place in the beginning of study year three of the RCT, ensuring that routines were well-established and thereby less prone to change due to outside factors. The use of an experienced WOMBAT observer (EL) [26,28,37] is another strength of the study, most likely favoring precision but not the accuracy of the measurements. Other time and motion studies have reported acceptable inter-observer reliability above 85% consensus, indicating that some variations between recordings are expected [24,25]. The conducted debrief revealed that some of the nurses hesitated to contact the clinical pharmacists when data was recorded, probably resulting in an underestimation of interruptions, multitasking, and possibly affecting verbal communication time. Neither can we disregard the possibility that having an observer present may have affected the participating pharmacists [38].

Conclusion

The clinical pharmacists spent approximately the same amount of time performing clinical and administrative tasks when running an RCT. The theoretical costs of the intervention would be grossly over-estimated if clinical and administrative tasks were not differentiated.

The pharmacists devoted substantial time to performing medication reviews, which most likely reflect the research setting rather than the standard clinical practice behavior. This study highlights the importance of assessing time spent on different tasks when performing clinical services and that time and motion studies of clinical pharmacists in real-life geriatric ward settings are warranted.

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Appendices

Appendix 1

Appendix 1

Terms in Norwegian, translation based on Nishtalas list of alternative terms (see below).

Alternative terms used searching	Number of hits for each term
Antikolinerg	146
Antikolinergika	78
Acetylkolin	43
Kolinerg	52
Antimuskarinerg	5
Muskarinerg	8
ACH	3
Atropinlignende	3
Kolinolytisk	0
Kolinolytika	0
Parasympatisk	6
Parasympatolytic	4

List of alternative terms used for anticholinergics, Nishtala et al.

Obtained from Nishtala et.al., (2016) Anticholinergics: theoretical and clinical overview, Expert Opinion on Drug Safety, 15:6, 753-768, DOI: 10.1517/14740338.2016.1165664.

Synonyms/alternative terms used for 'anticholinergics'

Anticholinergics	Cholinergic receptor blocker
Anti-cholinergics	Cholinolytic agent
Acetylcholine antagonists	Cholinolytics
Acetylcholine receptor blocker	Meta cholinoreactive cell
Acetylcholine receptor blocking agent	Muscarinic antagonist
Acetylcholine receptor inhibitor	Muscarinic antagonists
Achr inhibitor	Muscarinic blocker
Agent, parasympathicolytic	Muscarinic blocking agent
Anticholinergic agent	Muscarinic receptor antagonist
Anticholinergic drug	Muscarinic receptor blocker
Antimuscarinic agent	Muscarinolytic agent
Antimuscarinic drug	Parasympathetic blocker
Atropinic agent	Parasympathetic blocking agent
Atropinic drug	Parasympathicolytic agent
Central anticholinergic	Parasympathicolytic drug
Cholinergic antagonist	Parasympatholytic
Cholinergic antagonists	Parasympatholytic agent
Cholinergic blocker	Parasympatholytic drug
Cholinergic blocking agent	Parasympatholytics
Cholinergic blocking drug	Parasympaticolytic agent
Cholinergic receptor antagonist	Parasympatolytic agent

Appendix 2

Appendix 2, Drugs included as AC/SED-drugs

General information

To avoid duplicates, drugs with both AC and SED properties were classified as AC in line with the original evaluation of DBI (Hilmer SN et al. A drug burden index to define the functional burden of medications in older people. Archives of internal medicine. 2007;167(8):781-7. **doi**:10.1001/archinte.167.8.781). Formulations with a systemic route of administration (injections, oral, transdermal and spray for systemic uptake) were included in the analysis.

Drugs with anticholinergic properties

Pharmacological substance	ATC WHO level 5	Also SED properties
Alimemazine	R06AD01	
Amitriptyline	N06AA09	Yes
Atropine	A03BA01	
Biperiden	N04AA02	Yes
Carbamazepine	N03AF01	Yes
Chlorprothixene	N05AF03	Yes
Clomipramine	N06AA04	Yes
Clozapine	N05AH02	Yes
Cyclizine	R06AE03	
Darifenacin	G04BD10	
Disopyramide	C01BA03	
Dronedarone	C01BD07	
Escitalopram	N06AB10	Yes
Fesoterodine	G04BD11	
Glycopyrronium Bromide	A03AB02	
Hydroxyzine	N05BB01	Yes
Hyoscyamine	A03BA03	
Levomepromazine	N05AA02	Yes
Loratadine	R06AX13	
Meclozine	R06AE05	
Mirtazapine	N06AX11	Yes
Nortriptyline	N06AA10	Yes
Olanzapine	N05AH03	Yes
Oxybutynin	G04BD04	
Oxycodone	N02AA05	Yes
Perphenazine	N05AB03	Yes
Prochlorperazine	N05AB04	Yes
Promethazine	R06AD02	
Quetiapine	N05AH04	Yes
Scopolamine	A04AD01	Yes
Solifenacin	G04BD08	
Trimipramine	N06AA06	Yes

Drugs with sedative properties

Pharmacological substance	ATC WHO level 5
Almotriptan	N02CC05
Alprazolam	N05BA12
Amisulpride	N05AL05
Aripiprazole	N05AX12
Baclofen	M03BX01
Brexpiprazole	N05AX16
Brivaracetam	N03AX23
Buprenorphin	N02AE01
Buspirone	N05BE01
Cariprazine	N05AX15
Chlorproethazine	N05AA07
Chlorpromazine	N05AA01
Citalopram	N06AB04
Clobazam	N05BA09
Clomethiazole	N05CM02
Clonazepam	N03AE01
Clonidine	N02CX02
Codeine	R05DA04
Codeine and acetaminophen	N02AJ06
Combinations	R05DA20
Dexmedetomidine	N05CM18
Diazepam	N05BA01
Doxepin	N06AA12
Droperidole	N05AD08
Duloxetine	N06AX21
Eletriptan	N02CC06
Eslicarbazepine	N03AF04
Ethylmorphine	R05DA01
Felbamate	N03AX10
Fentanyl	N02AB03
Fluoxetine	N06AB03
Flupentixol	N05AF01
Fluphenazine	N05AB02
Flurazepam	N05CD01
Fluvoxamine	N06AB08
Fosphenytoin	N03AB05
Frovatriptan	N02CC07
Gabapentin	N03AX12
Haloperidol	N05AD01
Hydrocodone	R05DA03
Hydromorphone	N02AA03
Hyperici herba (St. John's Wort)	N06AX25
Ketobemidone	N02AB01
Ketobemidone og spasmolytics	N02AG02
Lacosamide	N03AX18
Lamotrigine	N03AX09
Levetiracetam	N03AX14
Lithium	N05AN01
Lorazepam	N05BA06
Loxapine	N05AH01
Loxapine	N05AH01

Lurasidone	N05AE05
Melatonin	N05CH01
Melperone	N05AD03
Meprobamate	N05BC01
Metoclopramide	A03FA01
Mianserin	N06AX03
Midazolam	N05CD08
Morphine	N02AA01
Naratriptan	N02CC02
Nitrazepam	N05CD02
Noscapine	R05DA07
Oxazepam	N05BA04
Oxcarbazepine	N03AF02
Paliperidone	N05AX13
Paroxetine	N06AB05
Passionflower	N05CM-
Penfluridol	N05AG03
Perampanel	N03AX22
Pethidine	N02AB02
Phenobarbital	N03AA02
Phenytoin	N03AB02
Pimozide	N05AG02
Pregabalin	N03AX16
Propiomazine	N05CM06
Reboxetine	N06AX18
Risperidone	N05AX08
Rizatriptan	N02CC04
Rufinamide	N03AF03
Scopolamine	N05CM05
Sertindole	N05AE03
Sertraline	N06AB06
Sumatriptan	N02CC01
Tapentadol	N02AX06
Theofylline	R03DA04
Thioridazine	N05AC02
Tiapride	N05AL03
Topiramate	N03AX11
Tramadol	N02AX02
Tramadol and acetaminophen	N02AJ13
Triazolam	N05CD05
Trifluprомazine	N05AA05
Valerianae radix	N05CM09
Valproic acid	N03AG01
Venlafaxine	N06AX16
Vigabatrin	N03AG04
Vortioxetine	N06AX26
Ziprasidone	N05AE04
Zolmitriptan	N02CC03
Zolpidem	N05CF02
Zonisamide	N03AX15
Zopiclone	N05CF01
Zuclopenthixol	N05AF05

Drugs with both anticholinergic and sedative properties, classified as AC.

Pharmacological substance	ATC WHO level 5
Amitriptyline	N06AA09
Biperiden	N04AA02
Carbamazepine	N03AF01
Chlorprothixene	N05AF03
Clomipramine	N06AA04
Clozapine	N05AH02
Clozapine	N05AH02
Escitalopram	N06AB10
Hydroxyzine	N05BB01
Levomepromazine	N05AA02
Mirtazapin	N06AX11
Nortriptyline	N06AA10
Oxycodone	N02AA05
Olanzapine	N05AH03
Perphenazine	N05AB03
Prochlorperazine	N05AB04
Quetiapine	N05AH04
Scopolamine	A04AD01
Trimipramine	N06AA06

Appendix 3

Appendix 3 Comorbidities based on reimbursement codes from NoRPD.

	CCI categories	**ICD-10 reimbursement**	**ICPC reimbursement**
1	Myocardial infarction	I21-I23, -22	K75, -22
2	Congestive heart failure	I50; I11.0;	K77
3	Peripheral vascular disease	I70-I74; I77, -26	K92, K99,-26
4	Cerebrovascular disease	I60-I69; G45; G46	K89, K90, K91,
5	Dementia	F00-F03; F05.1; G30	P70-
6	Chronic pulmonary disease	J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3	R78, R79, R95, R96, R99
7	Rheumatologic disease	M05; M06; M30-36	L88,
8	Ulcer disease	K22.1; K25-K28	D84-D86
9	Mild liver disease	B18; K70.0-K70.3; K70.9; K71; K73; K74; K76.0	D 72, D97
10	Diabetes mellitus	E10.0, E10.1; E10.9 E11.0; E11.1; E11.9	T89, T90
11	Hemiplegia	G81; G82	
12	Renal disease	I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61	K87, U88, U99
13	Diabetes mellitus with chronic complications	E10.2-E10.8 E11.2-E11.8	
14	Any tumor (including leukemia and lymphoma)	C00-C75, C81-C90, C91-C96, -50, -53	A79, B72-74, D74-77, N74, L71, R84, S77, Y77, Y78, X76, X77, U75, -50, -53,
15	Moderate/severe liver disease	B15.0; B16.0; B16.2; B19.0, K70.4; K72; K76.6; I85	
16	Metastatic solid tumor	C76-C80, -52, -90	-52, -90
17	AIDS	B20-B24 Also: -04 plus ATC: J05AE (all) J05AF05, 06, 07, 09 J05AG (all) J05AR (all) J05AX08, 09, 12	B90 Also: -04 plus ATC: J05AE (all) J05AF05, 06, 07, 09 J05AG (all) J05AR (all) J05AX08, 09, 12

Appendix 4

Appendix 4. The variable *Mental illness* (Paper I)

Category	**ICD 10 reimbursement codes**	**ICPC reimbursement codes**
Psychiatric disorders (and behavioral disturbances, and addiction to substances (F))	F05.0 F05.8 F05.9 F06-F51 (alle) F54-55 F59-63, F67-69 F90-98 -F2, F3, F4	P15-P19 P71-P99 -70 -72 -73 -74

This variable includes mental illnesses not covered by the CCI, based on reimbursement codes from NoRPD.

Not included in this variable:

Sexual dysfunction, dysfunction in connection with childbirth, sexual development and sexuality, mental retardation, developmental disorders.